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Editorial

SOME REMARKS ON THE MANAGEMENT OF NEUROSYPHILIS

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THE management of neurosyphilis depends upon an understanding of the progress of the infection. Invasion of the nervous system occurs early in the course of the infection, usually as a part of the spirochetemia of the secondary stage, and almost always within the first 2 years of infection. Except for the occasional appearance of syphilitic meningitis, neurosyphilis is asymptomatic, and is recognizable only by routine examination of the spinal fluid.

While it is certainly a truism that the best management of neurosyphilis is its prevention by the administration of penicillin during the treatment of early syphilis, there is nevertheless an occasional patient in whom the spinal fluid becomes or remains positive after an initial course of penicillin for early, or relatively early syphilis. It is therefore still desirable to examine the spinal fluid of all patients with syphilis. In early syphilis, this should be done ideally one year after treatment, while in late syphilis the examination of spinal fluid should precede treatment. If, however, a negative test of the spinal fluid has been obtained in a patient with syphilis of over 2 years' duration, repeat examination of the spinal fluid in the absence of reinfection is never necessary because, if the central nervous system is to be invaded at all, the infection occurs during the first 2 years of the disease.

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An adequate examination of the spinal fluid must include a careful cell count, total protein, and quantitative Wassermann test. The type of zone precipitation observed in the colloidal curve is actually of no significance in the differentiation of the clinical types of neurosyphilis. Any type of curve can be produced by any kind of meningeal irritation. In the absence of a positive spinal fluid Wassermann reaction, pleocytosis, protein elevation, and an abnormal colloidal curve indicate merely meningeal irritation, but not its etiology.

Flocculation tests on spinal fluid are less satisfactory than the Wassermann test. No direct conclusions as to the type of neurosyphilis can be drawn from the quantitative spinal fluid Wassermann test, but a strongly positive Wassermann reaction is usual in paresis.

Spinal fluids are classified as active or inactive on the basis of the cell count and total protein. This classification is especially useful in posttreatment observation because, under the influence of treatment, the cell count is the first to return to normal, protein next, and finally but much more slowly the colloidal curve and Wassermann reaction.

False positive spinal fluid Wassermann reactions occur with great infrequency. We have observed them in tuberculous meningitis, benign lymphocytic meningitis, and meningococcal meningitis. They have also been reported in subarachnoid hemorrhage, poliomyelitis, and other types of acute bacterial meningitis. In persons known to have syphilis without neurosyphilis temporary transfer of reagin from blood to spinal fluid may occur during the course of meningeal infection of other etiology.

Neurosyphilis may remain asymptomatic throughout the lifetime of the patient; indeed, in rare cases, the spinal fluid may spontaneously revert to negative. Or, the neurosyphilis may progress, usually after a period of years, to one of a complex group of clinical syndromes which differ widely from each other in symptoms and in prognosis. From a neuropathologic standpoint, meninges, blood vessels, and parenchyma are all involved, and the clinical diagnosis depends upon whether the predominant process is meningovascular or parenchymatous, inflammatory or degenerative. Those clinical syndromes which are predominantly meningeal and inflammatory, that is, all instances of early asymptomatic neurosyphilis, most instances of late asymptomatic neurosyphilis, syphilitic meningitis, and a large group of late unclassified neurosyphilis, respond well to treatment. To the extent, however, to which parenchymatous degeneration or involvement of large blood vessels predominates, as in paresis, tabes, primary optic atrophy, Erb's paraplegia, or focal vascular neurosyphilis, the clinical results of treatment are limited by the pre-existing amount of parenchymal damage, since no treatment can repair destroyed nerve cells. Irreparable neuraxis damage may have occurred prior to treatment and clinical manifestations may persist even though the active syphilitic process has been arrested by treatment. Dattner and Thomas have shown that following successful therapy of all types of neurosyphilis cell counts decline to normal usually within 6 months. Thus, a normal cell count is the earliest and most sensitive index of the arresting of the process. Total protein values are not nearly so sensitive an indicator, and protein elevation may persist for years in the absence of progression. The persistence of

positive colloidal reactions and Wassermann tests of the spinal fluid does not necessarily indicate a persistence of active infection. Reactivation of the neurosyphilitic process is usually indicated by a persistent or recrudescent spinal fluid cell count elevation.

Once the diagnosis of neurosyphilis is made, the treponemicidal drug of choice for all the clinical manifestations, as well as for asymptomatic cases, is penicillin and penicillin alone. Fever therapy is today only of historical interest. If a history of previous hypersensitivity to penicillin is obtained, it is necessary to evaluate this history carefully by detailed inquiry to ascertain its validity. It is also necessary to determine by detailed examination of the patient just how important it is to give maximal antisyphilitic therapy. It is by evaluation of these two factors on an individual basis that the therapy is determined. As an example, I might cite the case of a person with tabes with primary optic atrophy and an active spinal fluid with elevated cell count and protein who gives a questionable history of a rash after previous penicillin therapy. In such a patient, the proper course of action is probably to start the patient on steroids and shortly thereafter begin penicillin in adequate dosage, decreasing steroid dosage gradually over a week or two after the penicillin treatments have been completed, watching carefully for possible appearance of allergic reaction so that steroids may be reinstituted if necessary. On the other hand, in a patient with a clear-cut history of generalized urticaria, fever, and arthritic swelling from previous penicillin, one of the broad-spectrum antibiotics, either erythromycin or one of the tetracycline group, may be used in dosage of 2 Gm. a day for approximately 20 days. It is well documented that these antibiotics will at least reduce the cell count of the spinal fluid to normal, and in a few patients who have been followed over a sufficient period of time the disease has not progressed clinically.

In neurosyphilis the Herxheimer reaction is sometimes of great practical importance. Its frequency of incidence is directly proportional to the elevation of the cell count in the cerebrospinal fluid. In paresis there may be a temporary exacerbation of the paretic process resulting in delusion, hallucinations, or paranoid trends, or even status epilepticus, which can lead to death. In asymptomatic neurosyphilis with an active fluid a psychosis may temporarily appear. These reactions cannot be avoided by the initation of treatment with small doses of penicillin. Although I have not had personal experience, the French literature recommends the use of adrenal steroids to prevent Herxheimer reactions in active neurosyphilis. As a rule, with adequate general medical care, including sedation or anticonvulsant drugs as indicated, and maintenance of fluid and nutritional balance, any temporary ill effects of the Herxheimer reaction may be successfully countered.

In a paretic patient known to have had seizures previously, anticonvulsant drugs, such as Dilantin and phenobarbital should be given before and during penicillin therapy. In tabes dorsalis, Herxheimer reactions, particularly in the form of exacerbation of lightning pains, are not uncommon, but are ordinarily not serious. Exacerbations of bladder difficulties, if they occur at all, do so with much less frequency than they did during fever therapy.

In 1946, Clarke and I studied the prognosis of asymptomatic neurosyphilis

with metal chemotherapy. Among 467 patients, the probability of developing clinical neurosyphilis by the tenth year of observation was 15.8 per cent. In 1956, a cooperative study of 765 patients with asymptomatic neurosyphilis showed, following penicillin therapy, a probability of progression to clinical neurosyphilis of only 3.3 per cent by the seventh year after treatment. These progressions with but one exception consisted of minor neurological changes and none of the patients were incapacitated. This study indicates that penicillin is quite capable of curing asymptomatic neurosyphilis in almost all cases. Re-treatment on the basis of persistent positive laboratory findings alone is not recommended unless the cell count remains significantly elevated for 6 months after treatment, or increases markedly after approaching normal or near normal following treatment.

Paresis has not been observed to develop following the penicillin treatment of asymptomatic neurosyphilis. From the results of a cooperative study of 1,086 paretic patients, the majority of whom were followed for more than 5 years, it can be stated that the early diagnosis and prompt penicillin treatment of incipient paresis result in clinical remission with ability to work in more than 80 per cent of the patients and prevent practically all deaths from neurosyphilis. Even the institutionalized patient with advanced disease has one chance out of three of deriving improvement and rehabilitation for work. In contrast to the dire prognosis of untreated paresis, only 9 per cent of penicillin-treated paretic individuals have died of paresis 10 years after treatment. The effects of treatment on the individual signs and symptoms of paresis are in general strikingly beneficent. In the majority of cases, however, abnormalities of speech, insight, calculation, judgment, and general information do not entirely disappear. In paresis, as in neurosyphilis in general, respository penicillin is quite suitable. Although the minimal effective dose is unknown, our studies have suggested strongly that 6,000,000 units of procaine penicillin is ample in almost all cases. Although prolonged follow-up on a similar large number of patients with Bicillin therapy is not available, it is highly likely that a minimum of 4.8 million units of Bicillin is also quite satisfactory. In general, more than one course of penicillin is of no demonstrable additional value. Re-treatment with penicillin in paresis is indicated if the initial course of therapy was less than 6,000,000 units, especially if temporary clinical improvement on this course was followed by progression of disease, or if spinal fluid cell counts of five or more persist for one year following treatment. The essentially identical probability of death in patients who receive one course and patients who receive more than one course of treatment is strong evidence against the value of routinely repeated courses of penicillin for the treatment of general paresis. Biologic relapse in neurosyphilis occurs with extreme rarity more than 2 years after treatment has produced a persistently inactive spinal fluid.

The clinical response to treponemicidal therapy in tabes dorsalis is erratic, and under certain circumstances ancillary measures assume equal importance. The acute gastric crisis is best treated by the administration of intravenous fluids and sedation. Atropine may be of some value. Narcotics often give dramatic relief but should be used with discretion because of the grave danger of addiction, Prefrontal lobotomy may be considered as a last resort and, in skilled hands,

chordotomy is sometimes of value. Lightning pains may usually be controlled with codeine and the ordinary oral analgesics, but one of the stronger parenteral narcotics may be necessary. In tabetic ataxia a trained physiotherapist may re-educate the patient sufficiently to permit unaided ambulation.

Management of the tabetic bladder is of grave concern since ascending urinary tract infection is a frequent complication. The patient should be instructed to empty the bladder, with the aid of gentle lower abdominal pressure, every 3 hours by the clock. If pyuria is present, appropriate therapy should be instituted after urine cultures and sensitivity tests of isolated organisms are obtained. Urologic consultation with estimation of bladder capacity, residual urine, and cystometrogram, as well as tests of kidney function and intravenous pyelography, is often indicated. Transurethral prostatic resection is frequently followed by gratifying relief of symptoms since weakening of the vesical neck by surgical means allows the weak detrusor muscle to empty the bladder more efficiently.

In the Charcot joint, surgical therapy is almost always disastrous and conservative orthopedic bracing with protection of the joint from damage incidental to use is the proper management.

In primary optic atrophy, which so frequently accompanies tabes, the clinical results of therapy are extremely erratic but it is clear that penicillin is just as good as fever therapy. In some cases, progression can be arrested.

There is one manifestation of neurosyphilis which does not respond to penicillin therapy and that is the nerve deafness of late congenital syphilis. The scantiness of postmortem data permits no certain conclusions about the pathology or even the anatomic site of the lesion in this condition; I have wondered whether it might not be a hypersensitivity phenomenon analogous to interstitial keratitis. It was this possibility which induced me to treat the first such patient with prednisone in the autumn of 1956. The results of therapy were dramatic and the case was reported in *The Journal of the American Medical Association*, in August of 1958. Since that time I have had the opportunity of treating a total of 14 patients with the nerve deafness of congenital syphilis, with results carefully evaluated by detailed and repeated audiometric study at The Johns Hopkins Hearing and Speech Clinic before and after therapy. The response to treatment in the majority of these patients has been dramatic. It is still too early to say whether these results will be sustained after therapy has been terminated, because most of the patients are still being treated, but several have maintained their hearing for periods of months to more than a year after treatment was stopped. I have tried steroids on several patients with primary optic atrophy without demonstrable effect.

In summary, the proper management of neurosyphilis consists, first, of its prevention by the penicillin treatment of early syphilis, second, of its recognition by routine examination of cerebrospinal fluid, third, of its adequate treatment with 6 to 10 million units of penicillin or 4.8 million units of Bicillin, fourth, of adequate clinical and spinal fluid follow-up, and, finally of re-treatment for persistent or recrudescent pleocytosis in the spinal fluid, and in rare cases for clinical progression.

Endocrinology

THE EFFICIENCY OF SCREENING TESTS FOR DIABETES

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THE productivity of screening or the narrowing down of large groups of apparently well people to those who may best benefit from the diagnostic process depends chiefly on three factors: (1) the prevalence of unknown disease in the group being screened; (2) the reliability of the screening test; and (3) the efficiency of the test. *Reliability* here refers to the extent to which the results of the test may be reproduced by a laboratory technician of average training. *Efficiency* (validity) here refers to the frequency of confirmation of the test by accepted diagnostic procedure at a given level of reliability. This paper will be limited to the quantification of the efficiency of screening tests for diabetes mellitus as case-finding procedures.

From 1954 through 1957, a study was made by the Public Health Service, United States Department of Health, Education, and Welfare, at the Outpatient Department of Boston City Hospital, Boston, Massachusetts. The purpose of the investigation was to determine the efficiency of a number of blood and urine screening tests under timed and controlled conditions of food intake. This study was a further development of an earlier study reported by Kurlander, Iskrant, and Kent,[1] which was based on 273 persons screened under less closely controlled circumstances. Preliminary reports on the present study have appeared in two published summaries.[2,3]

The efficiency of a screening test—previously defined as the frequency of confirmation by accepted diagnostic procedure—is measured in terms of sensitivity and specificity. *Sensitivity* is defined as the ability of the test to classify as positive those who have the condition or disease being screened for in an apparently well population. It is expressed as the percentage screening positive of the total true previously unknown cases of the disease. *Specificity* is defined as the ability of the test to classify as negative those who do not have the condition

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or disease for which they are being screened. It is expressed as the percentage screening negative of those who do not have the disease in the group being screened. Sensitivity and specificity are shown diagrammatically in Fig. 1 as applied to diabetes.

SCREENING RESULT	TRUE DISEASE CLASSIFICATION OF APPARENTLY WELL POPULATION	
	Unknown Diabetics	Nondiabetics
Positive	Positive Diabetics	Positive Nondiabetics**
Negative	Negative Diabetics*	Negative Nondiabetics
Total	Total Unknown Diabetics	Total Nondiabetics

*False - negatives

**False - positives

$$\text{Sensitivity} = \frac{\text{Positive Diabetics}}{\text{Total Unknown Diabetics}} \times 100$$

$$\text{Specificity} = \frac{\text{Negative Nondiabetics}}{\text{Total Nondiabetics}} \times 100$$

Fig. 1.—Schematic presentation of sensitivity and specificity.

Many screening tests are based on quantitative or semiquantitative measurements. For example, in screening for diabetes, blood sugar levels are frequently used to screen out from a group those most likely to have diabetes. A screening level is selected at or above those glucose readings which are considered to be abnormal (positive) and below those which are considered to be normal (negative). Any number of levels might be selected as the screening level. The percentage of persons considered positive by the test is greater at lower screening levels. Since a number of factors affect the amount of glucose present in the blood, and since diabetes is a complex metabolic disease, it is not possible to select a single screening level which would result in only diabetics being considered as positive and only nondiabetics being considered as negative. If such a screening level were

possible it would be said to be 100 per cent sensitive and 100 per cent specific. In practice, the lower the screening blood sugar level, the more sensitive, and less specific is the test; the higher the screening level, the less sensitive, and more specific is the test.

In order to quantify sensitivity and specificity, it is necessary to know the true composition of the population with respect to diabetes. Therefore each subject must receive a complete independent diagnostic workup regardless of screening test results.

METHOD OF STUDY

Persons seeking care at the Medical Clinic, Outpatient Department of the Boston City Hospital, were sent to the Metabolic Clinic after completion of their original purpose for visiting the Medical Clinic. Only the first few patients of any clinic day who were afebrile, not acutely ill, and had sufficient time were referred. The composition of the study population by age, race, and sex, is shown in Table I.

TABLE I. STUDY POPULATION BY AGE, RACE, AND SEX

AGE	TOTAL	WHITE MALE	WHITE FEMALE	NONWHITE MALE	NONWHITE FEMALE
Under 25	9	1	4	2	2
25 – 34	50	11	19	1	19
35 – 44	82	27	38	2	15
45 – 54	146	38	65	9	34
55 – 64	165	39	96	8	22
65 – 74	122	57	43	9	13
75 +	21	7	10	2	2
Total	595	180	275	33	107

The physician in the Metabolic Clinic explained to the person referred the time required for the tests, the tests to be given, and the need for return visits. From cooperating individuals, a urine specimen was obtained and a sample of venous blood drawn. In an attempt to simulate various screening conditions, particularly with regard to lapse of time since food intake, a meal designed to approximate the average breakfast or light lunch was given. This test meal consisted of a sandwich containing two slices of bread, 5 Gm. of butter, and 60 Gm. of cheese; 6 ounces of orange juice; and three filled cookies. The composition was approximately 74 Gm. of carbohydrate, 18 Gm. of protein, and 23 Gm. of fat. A check was made to see that all the food was eaten. Additional venous blood and urine samples were obtained at 1, 2, and 3 hours after eating (timed from the beginning of the test meal). During this first visit, dietary information and a routine medical history were obtained.

At the end of the first visit an appointment was made for a second visit from 3 to 21 days later. Instructions were given by a nutritionist, urging the participant to eat a diet which would have at least 250 Gm. or more of carbohydrate per day for 3 days prior to the second visit. The nutritionist advised the

participant how this dietary level could be attained. The subject was instructed to take nothing by mouth after midnight the day before the second visit.

The fasting participant returning at the second visit was given a 100 Gm. oral glucose tolerance test with blood and urine samples collected prior to ingestion of 100 Gm. of glucose and at one-, two-, and three-hour intervals after. At this visit a physical examination with special reference to signs and symptoms of diabetes was carried out.

On each blood specimen drawn at screening the following blood sugar tests were run for evaluation: Somogyi-Nelson,[4] Folin-Wu,[5] Anthrone,[6] and Wilkerson-Heftmann[7] (using both the Clinitron and the Test Kit at 130 mg. per 100 ml.). The urine sugar tests included Benedict's,[8] Clinitest,* Galatest,† Dreypak,[9] Tes-Tape,‡ and Clinistix.§

Test procedures followed the author's or manufacturer's directions. In the Somogyi-Nelson procedure a 1:10 dilution was used in preparation of filtrate. In the Folin-Wu analysis a dilution with water was made 10 minutes after the addition of phosphomolybdic acid reagent, and the densities were determined 20 minutes after the dilution.

The diagnosis of diabetes was made on the basis of a set of criteria established by a group of consultants to the study. These included Dr. Leo P. Krall, Staff of Joslin Clinic, Boston, Massachusetts; Dr. Arnold Lazarow, Professor of Anatomy, University of Minnesota; Dr. C. N. H. Long, Professor of Physiology, Yale University School of Medicine; Dr. F. D. W. Lukens, Professor of Medicine and Director, George S. Cox Medical Research Institute, University of Pennsylvania; Dr. Alexander Marble, Assistant Clinical Professor of Medicine, Harvard University, Staff of Joslin Clinic; Dr. Henry T. Ricketts, Professor of Medicine, University of Chicago; Dr. Richard P. Stetson, Area Director of Professional Services, Veterans Administration, Boston, Massachusetts; and Dr. DeWitt Stetten, Jr., Associate Director in Charge of Research, National Institute of Arthritis and Metabolic Diseases. The diagnostic criteria decided upon by this group were based solely on the results of the 100 Gm. oral glucose tolerance test using the Somogyi-Nelson method and are as follows:

TIME AFTER GLUCOSE	MINIMUM READING CONSIDERED POSITIVE (MG. PER 100 ML.)
Fasting	110
1 hour	170
2 hours	120
3 hours	110

Diabetes was diagnosed if 3 or more consecutive readings equaled or exceeded the minimum value shown above or if the fasting and three-hour readings equaled or exceeded the minimum value. A point system which gives the same result

*Clinitest, a copper sulfate reagent tablet for urine sugar determinations, manufactured by the Ames Company, Inc., Elkhart, Ind.

†Galatest, a bismuth-oxychloride powder for urine sugar analysis, manufactured by the Denver Chemical Mfg. Co., New York, N. Y.

‡Tes-Tape, a urine sugar analysis paper, manufactured by Eli Lilly & Co., Indianapolis, Ind.

§Clinistix, an enzyme test of urine sugar utilizing reagent strips, manufactured by the Ames Company, Inc., Elkhart, Ind.

may be used in which the fasting and three-hour readings count 1 point each when positive and the one- and two-hour readings count ½ point each when positive. A total of 2 points is necessary for the diagnosis of diabetes.

RESULTS

A total of 595 persons were studied with the screening and diagnostic procedures as described. Not all persons received all tests at all hours; 580 persons had the blood tests at all hours, and 515 persons had the urine tests at all hours.

TABLE II. SOMOGYI-NELSON BLOOD TEST (VENOUS) SENSITIVITY AND SPECIFICITY FOR DIABETES AT DIFFERENT SCREENING LEVELS, BY HOURS AFTER TEST MEAL

BLOOD SUGAR LEVEL CONSIDERED POSITIVE (MG. PER 100 ML.)	BEFORE TEST MEAL		AT 1 HOUR AFTER TEST MEAL		AT 2 HOURS AFTER TEST MEAL		AT 3 HOURS AFTER TEST MEAL	
	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.
70	95.7	11.0	100.0	8.2	98.6	8.8	94.3	8.6
80	91.4	36.3	97.1	22.4	97.1	25.5	91.4	34.7
90	82.9	65.7	97.1	39.0	94.3	47.6	82.9	67.5
100	65.7	84.7	95.7	57.3	88.6	69.8	70.0	86.5
110	54.3	92.7	92.9	70.6	85.7	84.1	60.0	95.3
120	50.0	96.7	88.6	83.3	71.4	92.5	51.4	98.2
130	44.3	99.0	78.6	90.6	64.3	96.9	48.6	99.8
140	37.1	99.6	68.6	95.1	57.1	99.4	41.4	100.0
150	30.0	99.8	57.1	97.8	50.0	99.6	32.9	100.0
160	25.7	99.8	52.9	99.4	47.1	99.8	28.6	100.0
170	25.7	99.8	47.1	99.6	42.9	100.0	28.6	100.0
180	22.9	99.8	40.0	99.8	38.6	100.0	28.6	100.0
190	21.4	100.0	34.3	100.0	34.3	100.0	24.3	100.0
200	17.1	100.0	28.6	100.0	27.1	100.0	20.0	100.0

TABLE III. FOLIN-WU BLOOD TEST (VENOUS) SENSITIVITY AND SPECIFICITY FOR DIABETES AT DIFFERENT SCREENING LEVELS, BY HOURS AFTER TEST MEAL

BLOOD SUGAR LEVEL CONSIDERED POSITIVE (MG. PER 100 ML.)	BEFORE TEST MEAL		AT 1 HOUR AFTER TEST MEAL		AT 2 HOURS AFTER TEST MEAL		AT 3 HOURS AFTER TEST MEAL	
	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.
70	—	—	—	—	—	—	—	—
80	100.0	1.6	—	1.6	100.0	1.2	100.0	1.0
90	95.7	8.2	100.0	8.8	98.6	7.3	97.1	6.1
100	85.7	33.9	98.6	21.4	97.1	25.3	92.9	34.5
110	81.4	67.1	98.6	38.4	92.9	48.4	81.4	67.8
120	67.1	82.2	97.1	55.9	88.6	68.2	68.6	86.5
130	55.7	92.7	92.9	70.2	81.4	82.4	60.0	94.3
140	50.0	96.3	85.7	81.4	74.3	91.2	57.1	98.2
150	44.3	98.8	80.0	90.4	64.3	96.1	48.6	99.6
160	35.7	99.6	74.3	94.3	55.7	98.6	42.9	100.0
170	34.3	99.8	61.4	97.8	52.9	99.6	35.7	100.0
180	27.1	99.8	52.9	99.0	50.0	99.8	28.6	100.0
190	24.3	99.8	44.3	99.8	44.3	99.8	28.6	100.0
200	24.3	100.0	40.0	99.8	37.1	100.0	28.6	100.0

TABLE IV. ANTHRONE BLOOD TEST (VENOUS) SENSITIVITY AND SPECIFICITY FOR DIABETES AT DIFFERENT SCREENING LEVELS, BY HOURS AFTER TEST MEAL

BLOOD SUGAR LEVEL CONSIDERED POSITIVE (MG. PER 100 ML.)	BEFORE TEST MEAL		AT 1 HOUR AFTER TEST MEAL		AT 2 HOURS AFTER TEST MEAL		AT 3 HOURS AFTER TEST MEAL	
	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.
70	98.6	3.3	100.0	2.7	100.0	2.7	98.6	4.2
80	97.1	11.6	100.0	9.4	100.0	10.4	95.7	14.5
90	92.9	34.7	100.0	22.4	97.1	25.5	88.6	37.1
100	82.9	59.8	98.6	37.3	92.9	49.0	81.4	64.3
110	70.0	78.0	94.3	54.3	85.7	68.4	72.9	82.2
120	58.6	88.6	88.6	67.1	75.7	81.8	57.1	92.4
130	50.0	94.3	81.4	80.6	67.1	90.6	52.9	96.9
140	38.6	96.9	74.3	88.2	60.0	95.3	44.3	99.4
150	31.4	98.4	64.3	92.7	54.3	98.0	42.9	100.0
160	31.4	99.4	58.6	96.3	48.6	98.8	35.7	100.0
170	25.7	99.8	51.4	98.6	42.9	99.4	31.4	100.0
180	24.3	99.8	45.7	99.2	40.0	99.6	30.0	100.0
190	22.9	100.0	40.0	99.8	38.6	100.0	27.1	100.0
200	21.4	100.0	35.7	99.8	32.9	100.0	25.7	100.0

TABLE V. COMPARISON OF SOMOGYI-NELSON AND WILKERSON-HEFTMANN TESTS IN SENSITIVITY AND SPECIFICITY FOR DIABETES WITH 130 MG. PER 100 ML. CONSIDERED POSITIVE, BY HOURS AFTER TEST MEAL

SCREENING TEST	BEFORE TEST MEAL		AT 1 HOUR AFTER TEST MEAL		AT 2 HOURS AFTER TEST MEAL		AT 3 HOURS AFTER TEST MEAL	
	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.
Somogyi-Nelson	44.3	99.0	78.6	90.6	64.3	96.9	48.6	99.8
Wilkerson-Heftmann	45.7	98.2	78.6	90.0	61.4	95.3	47.1	99.4

Based on the diagnostic criteria established for the study, 72 previously unknown cases of diabetes were diagnosed (70 among those who had blood tests at all hours and 61 among those who had the urine tests at all hours).

Since the study population was divided into diabetics and nondiabetics by actual diagnosis, it was possible to compare the efficiency of the various tests in terms of their sensitivity and specificity at all possible screening levels and to compare the efficiency of each test according to the time since food intake.

Efficiency of Blood Testing.—Sensitivity and specificity of the blood sugar determination methods included in the study are presented in Tables II through V, based upon screening tests in 580 persons, 70 found to have diabetes and 510 without diabetes. Various blood sugar levels at or above which a screening test might be considered positive are shown with the corresponding sensitivity and specificity ratings. Ratings are shown for the pre-meal screening tests and for tests at one, two, and three hours following the test meal. Calculations are based on the 580 persons who had all blood tests at all hours.

The tables may be useful in selecting the screening level for a given program if it is kept in mind that a very high screening level will yield few false positives and a low level will result in more false positives but will detect a greater number of cases. More details on program application of these tables can be found in the Diabetes Program Guide, Public Health Service Publication No. 506.[3]

A comparison of the Wilkerson-Heftmann and Somogyi-Nelson methods is shown in Table V. Only the reagent tablets for screening at 130 mg. per 100 ml. were used in the study. Sensitivity and specificity of the Wilkerson-Heftmann method are not significantly different from the Somogyi-Nelson method at 130 mg. per 100 ml. Based on these results and other unpublished comparability studies in which different levels were used, it is concluded that ratings for 130, 160, and 180 mg. per 100 ml. screening levels of the Somogyi-Nelson test can be applied reliably to the Wilkerson-Heftmann method.

A comparison of the sensitivity-specificity results among the various blood tests at each hour in relation to the test meal is graphically portrayed in Fig. 2. It can be seen readily that the Anthrone method is consistently the least sensitive test at all levels of specificity and for all hours. The Somogyi-Nelson method appears to be slightly more sensitive than the Folin-Wu method, but the differences are very small and would have almost no practical value.

In Fig. 3 the relationship between specificity and sensitivity for the various hours in relation to the test meal is shown for each test. As can be seen from the charts, the test at 1 and 2 hours postprandially are very similar in sensitivity for the various levels of specificity. The test before the meal was least sensitive. This latter test was not a true fasting test. Some of the participants had breakfast prior to coming to the clinic; about one-sixth were in a fasting state of 6 hours' duration or more.

Efficiency of Urine Testing.—Tabular and graphic presentations of the relationship between specificity and sensitivity are shown for each urine test at the various times before and after the test meal in Table VI and in Figs. 4 and 5.

It should be noted that the urine test results are qualitative and that the five categories ranging from trace through 4+ are not representations of identical quantities of glucose or other reducing substances in the urine for every test. However, these points are ordinarily used semiquantitatively, and from them a sensitivity-specificity curve can be estimated. In approximating these curves no attempt has been made to extrapolate for sensitivity and specificity beyond the end points of trace and 4+ readings.

From Fig. 4 it can be seen that there are only small differences among the tests in sensitivity for any given level of specificity. Within the practical levels of specificity (90 to 100 per cent) there are no significant differences among the tests, nor is any one test consistently better than the others. On the basis of these data one may conclude that selection of the test should be made on factors other than efficiency.

In comparing the sensitivity and specificity by hours since food intake (Fig. 5), it can be seen that for almost all practical levels of specificity the order of sensitivity is: 2 hours, most sensitive; 3 hours, first hour, and before the test meal, least sensitive.

During the study two recent glucose oxidase methods of urine testing were added. While the number of cases is small, these tests, Tes-Tape and Clinistix, were more sensitive for equal specificity than was Benedict's solution. Because of the small sample size these results can be considered only indicative, rather than conclusive. Illustrative results are shown in Fig. 6 for 2 hours postprandial. Since the curves show the range of specificity and sensitivity, it may be observed

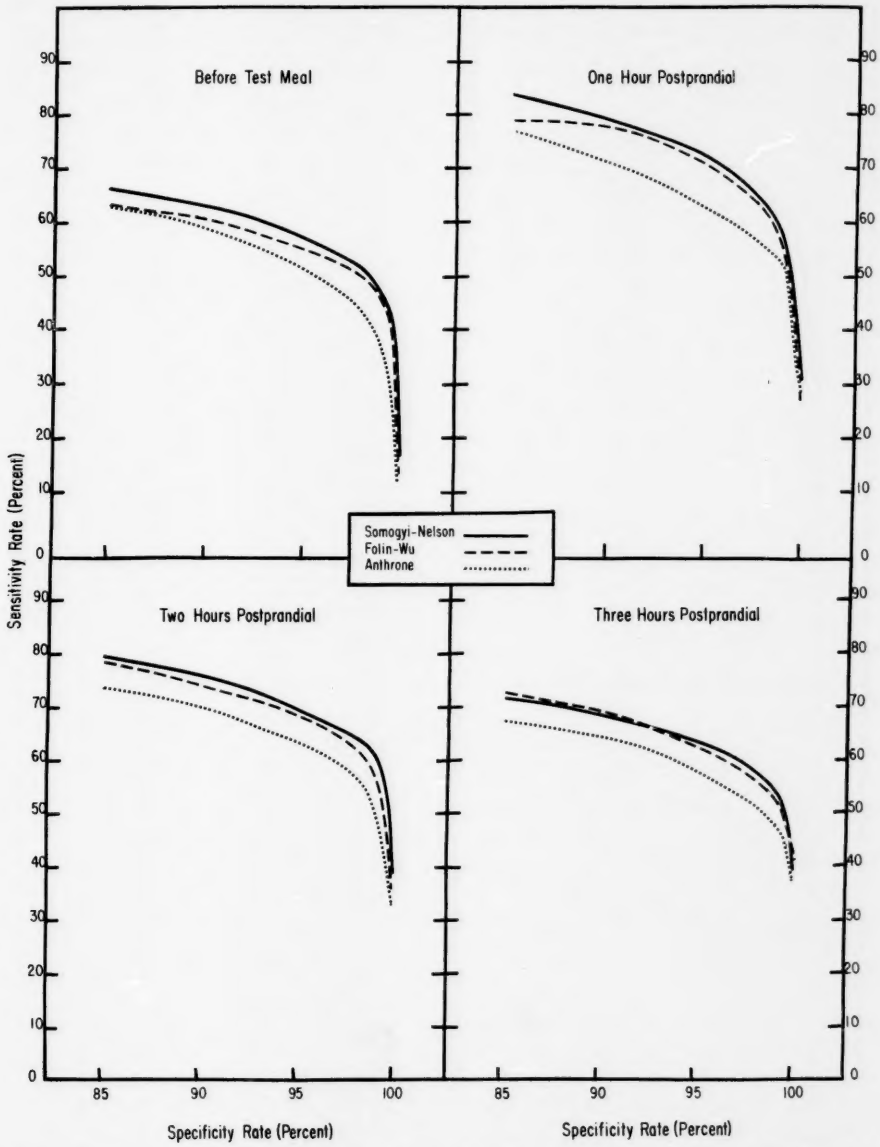

Fig. 2.—Sensitivity of blood sugar tests for diabetes at practical levels of specificity, by time since last food intake.

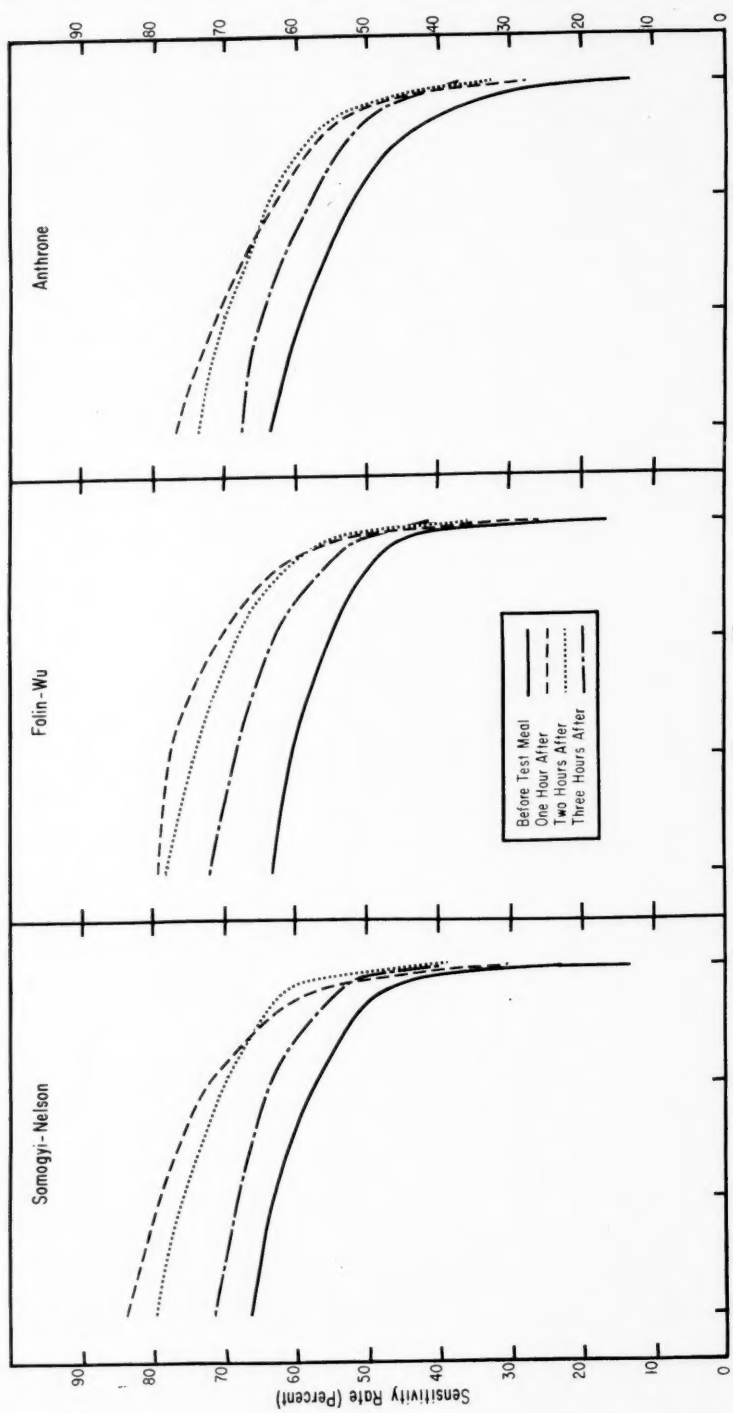

Fig. 3.—Comparison of sensitivity at controlled times since last food intake for blood sugar tests for diabetes, at practical levels of specificity.

Vol. 1
1961

from Fig. 6 that one has no choice but to use a highly specific test with the glucose oxidase method.

COMPARISON OF THE EFFICIENCY OF BLOOD AND URINE TESTING

This comparison of blood and urine screening results is limited to two standard tests: the Somogyi-Nelson blood sugar method and Benedict's urine sugar

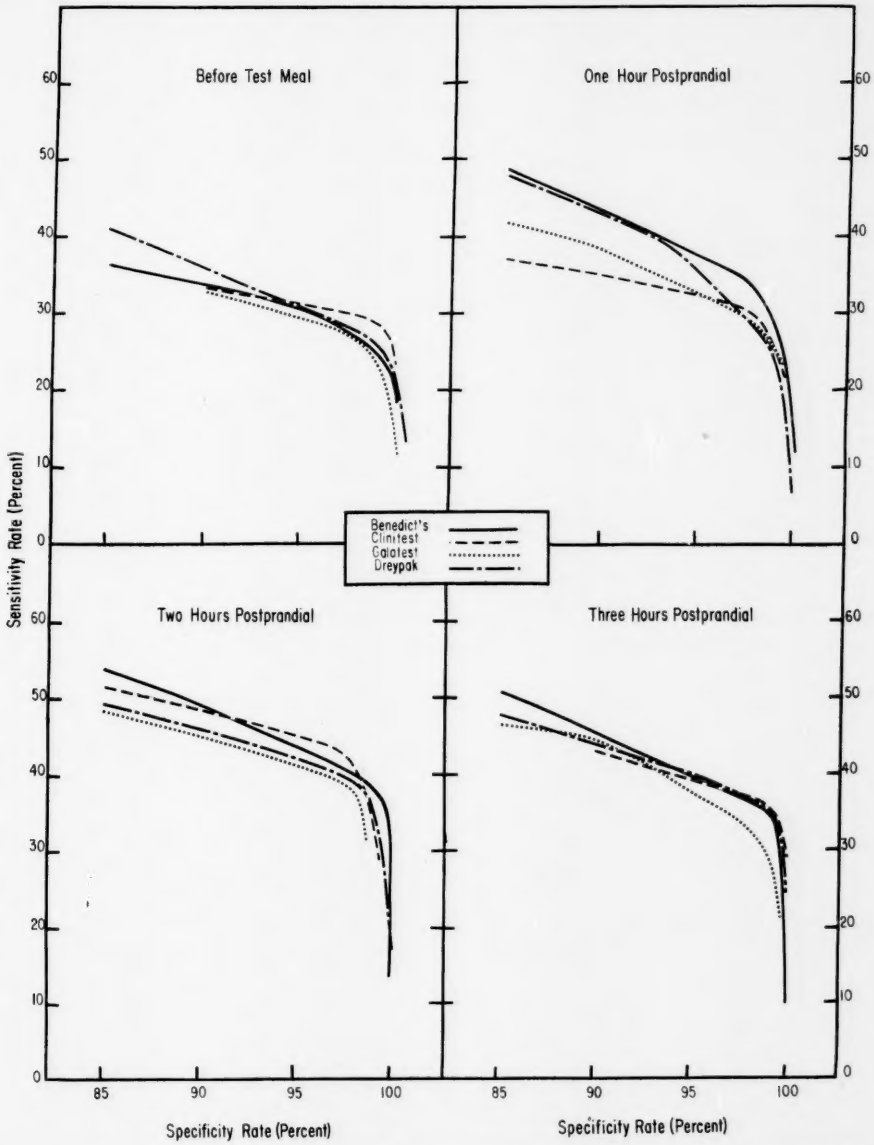

Fig. 4.—Sensitivity of urine sugar tests for diabetes for practical levels of specificity by time since last food intake.

method. Comparisons of each of these tests with other methods of testing blood or urine are shown in Figs. 2 and 4. In Fig. 7 the sensitivity of these two methods is compared for various levels of specificity at various times in relation to food intake.

For almost all levels of specificity, regardless of time in relation to food intake, the blood sugar method has a far greater sensitivity than the urine sugar method.

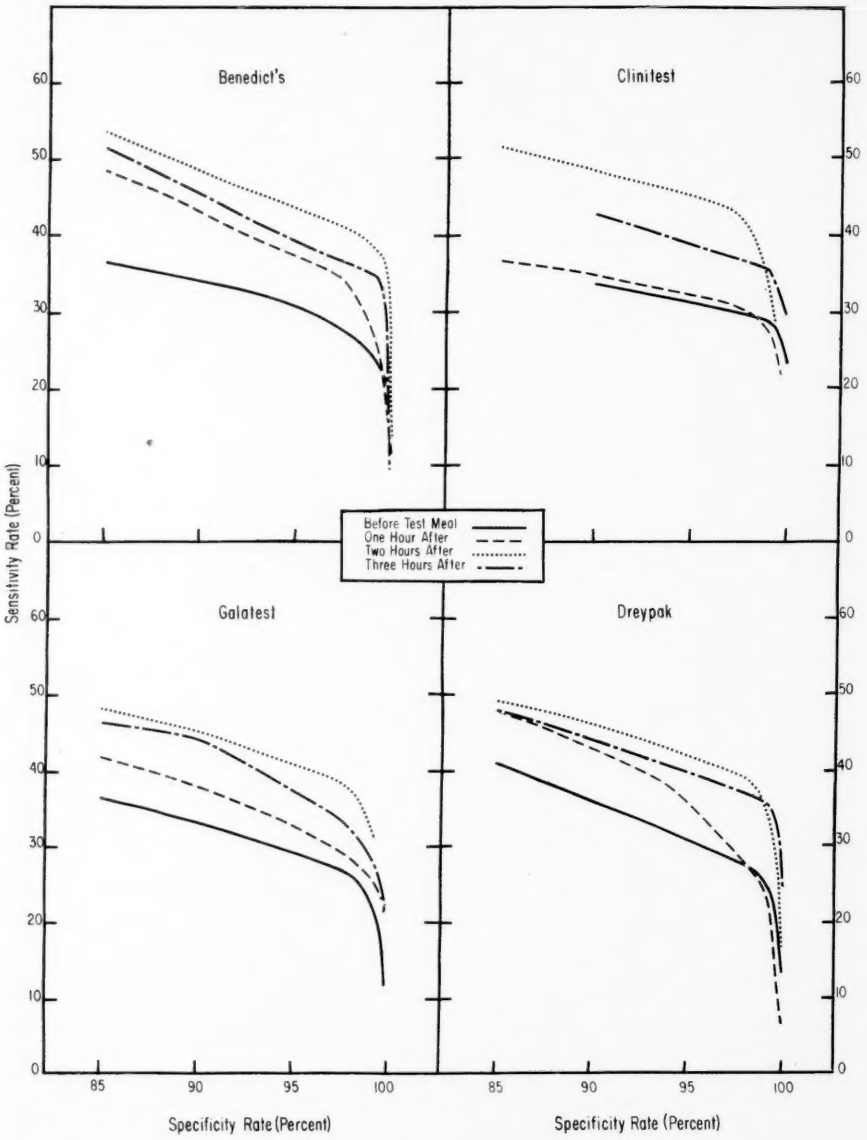

Fig. 5.—Comparison of sensitivity at controlled times since last food intake for urine sugar tests for diabetes, at practical levels of specificity.

The following practical example may help to illustrate the importance of these differences in results:

A screening program is to be undertaken to test 10,000 persons, among whom 200 previously unknown diabetics could be expected. It will be possible to test these persons at 2 hours postprandial (a good time for either blood or urine testing according to results for this study already noted). Specificity of 97 per cent can be obtained by either Benedict's urine sugar test considering 2+ or above as positive or the Somogyi-Nelson blood sugar method accepting 130 mg./100 ml. or above as positive. Using this urine sugar test one

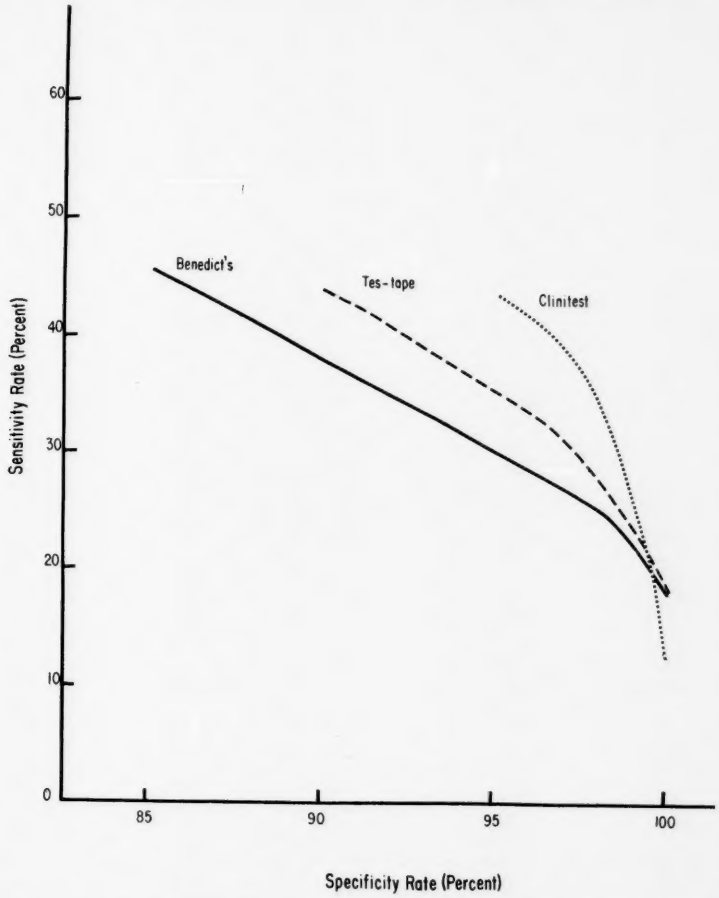

Fig. 6.—Sensitivity of glucose oxidase urine tests for practical levels of specificity compared to Benedict's tests at two hours postprandial.

could expect to identify 82 of the 200 expected diabetics (41 per cent sensitivity), but with the blood sugar method and level one could expect to identify 128 of the 200 diabetics (64 per cent sensitivity). One could expect that only 3 out of the 82 cases of diabetes detected by the urine test would have been missed by the blood sugar test at the screening levels used. The blood sugar method would screen out more than 1½ times as many cases of diabetes as the urine sugar method of equal specificity. Similar results can be obtained in comparing sensitivity for almost all practical levels of specificity.

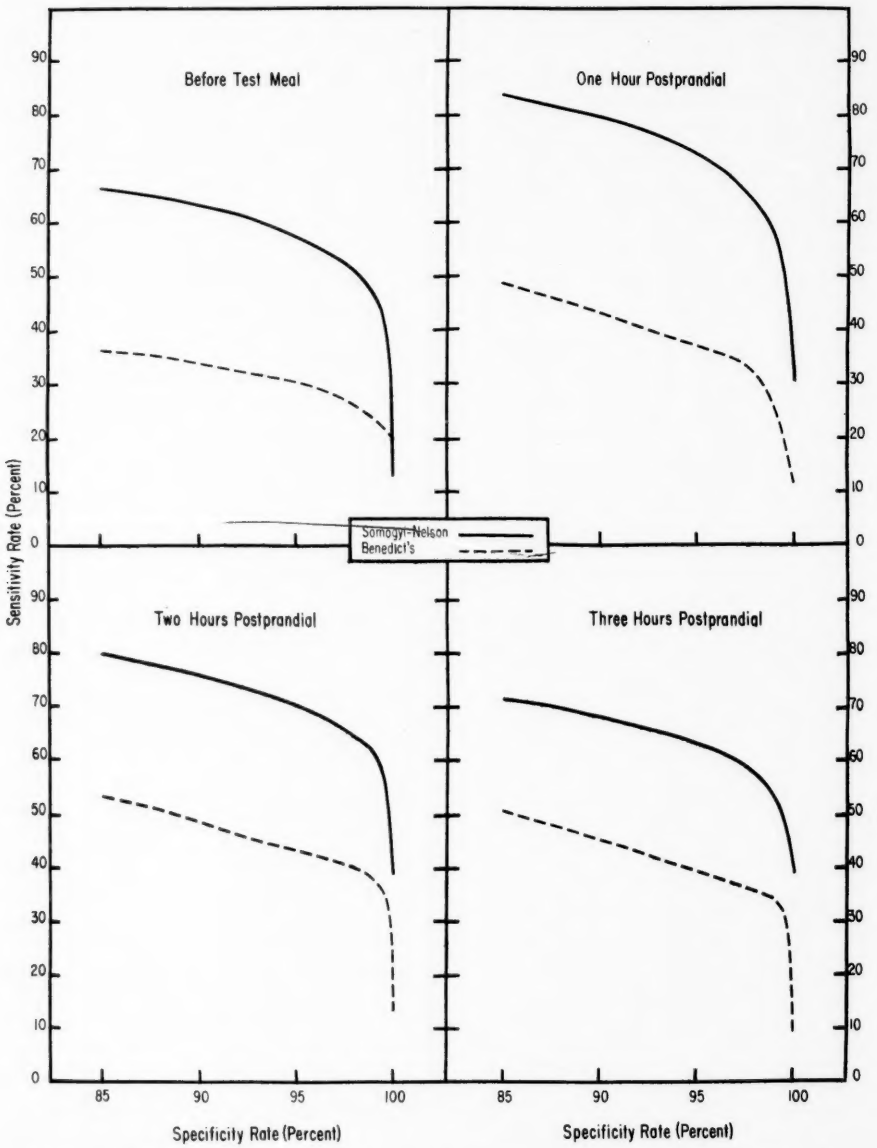

Fig. 7.—Comparison of sensitivity of the Somogyi-Nelson blood sugar and Benedict's urine sugar methods of screening for diabetes at practical levels of specificity by time since last food intake.

DISCUSSION

The application of the findings in this study to general population groups can be made only with caution and with the knowledge that certain assumptions have been made. The study group was not representative of the general population in several aspects.

The groups did not reflect the composition of the general adult population in race, sex, and age. There was a high proportion of illness, since most patients had come to the clinic for a specific complaint. Because these people were willing to participate, they may have been different in unknown ways from those clinic patients who refused to participate. The prevalence of diabetes was high. There were 12.1 per cent of the subjects with previously undiagnosed diabetes. While the method of determining the efficiency of the tests is not directly affected by the prevalence in the group under study, it may be affected indirectly by some of the factors accounting for prevalence differences; for instance, there was some evidence from the data that the efficiency of the tests was affected by age, although the influence was small.

Several factors probably accounted for the high rate of previously unknown diabetes found in this group. Unlike most programs for diabetes detection, each participant received a complete diagnostic workup and thus virtually no cases in the study group were missed. In our experience clinic population groups such as these have much higher diabetes rates than general population groups. Results

TABLE VI. SENSITIVITY AND SPECIFICITY RATINGS OF 4 URINE TESTS FOR DIABETES AT DIFFERENT SCREENING LEVELS, BY HOURS AFTER TEST MEAL

SCREENING TEST AND LEVEL ASSUMED TO BE POSITIVE	BEFORE TEST MEAL		AT 1 HOUR AFTER TEST MEAL		AT 2 HOURS AFTER TEST MEAL		AT 3 HOURS AFTER TEST MEAL	
	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.	SENS. % POS.	SPEC. % NEG.
Clinitest								
Trace	34.4	88.3	37.7	83.5	54.1	80.6	45.9	86.6
1+	29.5	98.7	31.1	96.9	44.3	96.5	36.1	98.5
2+	23.0	100.0	27.9	98.9	37.7	98.7	34.4	99.3
3+	19.7	100.0	24.6	99.3	31.1	99.1	29.5	100.0
4+	9.8	100.0	21.3	99.8	24.6	99.3	2.2	100.0
Galatest								
Trace	37.7	83.3	47.5	73.8	54.1	66.1	50.8	72.9
1+	29.5	95.0	37.7	90.3	47.5	87.2	44.3	90.7
2+	24.6	98.7	29.5	97.4	39.3	96.9	34.4	97.1
3+	18.0	99.6	26.2	99.1	34.4	98.7	31.1	98.7
4+	11.5	99.8	23.0	99.6	29.5	99.3	21.3	99.6
Benedict's								
Trace	42.6	73.6	68.9	54.4	88.5	34.6	80.3	51.1
1+	32.8	92.1	49.2	84.6	59.0	79.3	49.2	86.3
2+	21.3	99.8	34.4	97.4	41.0	97.4	34.4	99.3
3+	19.7	100.0	24.6	99.3	34.4	99.8	29.5	99.8
4+	4.9	100.0	11.5	100.0	13.1	100.0	9.8	100.0
Dreypak								
Trace	41.0	85.0	62.3	71.4	62.3	63.2	54.1	77.5
1+	27.9	97.8	39.3	93.4	45.9	90.3	39.3	95.8
2+	23.0	99.6	27.9	97.8	39.3	98.0	34.4	99.3
3+	13.1	100.0	24.6	99.3	32.8	99.3	24.6	100.0
4+	3.3	100.0	6.6	100.0	16.4	100.0	8.2	100.0

Only persons who had all 4 tests at all hours are included in this table—61 diabetics and 454 non-diabetics.

obtained by Kurlander and associates[1] in the previously mentioned study seem to confirm this. They gave glucose tolerance tests to a clinic population of generally similar composition and found about 9 per cent to have previously unknown diabetes. Other less significant contributing factors include the high prevalence area where the study was conducted, and the sexual and racial composition of the study group. In regard to age it may be pointed out that there appear to be differences in diabetes among older adult populations as compared to diabetes in juveniles and young adults. Onset appears to be insidious in the older person compared to the acute onset at earlier ages. Progression also appears to be slower in older persons.

Participants were not in a fasting state when given the blood and urine screening tests before the test meal. Thirty per cent had eaten within 2 hours prior to the test, 49 per cent had eaten within 2 to 4 hours, 3 per cent had eaten within 4 to 6 hours, and 17 per cent had not eaten within 6 hours. Whether this is representative of the general population is not known; therefore, the sensitivity-specificity results before the test meal may not be considered as identical to screening at random hours after food intake in a typical population. The influences of the status (with respect to food intake prior to the test meal) on sensitivity and specificity in the three hourly screening tests after the test meal are complicated by the Staub-Traugott[10] phenomenon and other factors. These factors, however, are operating to influence application of any practical screening program in a population where screening tests may be affected by the participants' successive intake of food such as breakfast, coffee breaks, snacks, and candy bars.

Another major consideration in interpreting and applying the data is the method of establishment of the diagnosis of diabetes. No attempt is made in this report to evaluate the diagnosis. The criteria are conservative as compared to other published criteria, and they represent the synthesis of opinion of a group of specialists; however, they may differ from criteria of physicians to whom positive participants in a screening program might be referred. It is recognized that the basis of diagnosis is not entirely independent of the screening methods compared.

CONCLUSIONS

1. The Somogyi-Nelson and Folin-Wu blood sugar test methods when applied to venous blood had roughly the same efficiency in this study. The Anthrone test was slightly less efficient than the other two methods.

2. No differences in efficiency were noted among the following urine sugar methods: Benedict's, Clinitest, Galatest, and Dreypak.

3. Preliminary results on a part of the study population, using glucose oxidase methods of urine testing, suggested that these test methods (Tes-Tape and Clinistix) were more sensitive for equal specificity than was Benedict's urine sugar test. One has no choice but to use a highly specific test with the glucose oxidase method.

4. Blood sugar tests were most efficient at 1 and 2 hours after eating; urine tests were most efficient at 2 hours after eating.

5. At 97 per cent specificity for both the Somogyi-Nelson blood sugar method and the Benedict urine sugar test method, the blood sugar method

screened out more than 1½ times as many cases of diabetes as the urine sugar method of equal specificity. Similar results can be obtained in comparing the sensitivity of blood and urine sugar tests for almost all practical levels of specificity.

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Grateful acknowledgment is made also of the cooperation given by the staff of the Outpatient Department, Boston City Hospital, and the patients whose participation made this study possible.

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Vol. 13
1961

THYROID CANCER AND THYROTOXICOSIS IN THE UNITED STATES: THEIR RELATION TO ENDEMIC GOITER

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THERE has been a clinical impression for many years that goiter predisposes not only to thyrotoxicosis but also to thyroid cancer. Statistical evidence supporting this hypothesis has been difficult to obtain. Surgical statistics[1-3] have indicated a high percentage of pre-existing goiter in cases of thyroid cancer and a high percentage of cancer in nodular goiter. As pointed out by Sokal[4] and Crile,[5] such figures represent only relative frequencies in a highly screened and selected group and tell us very little about the incidence of thyroid cancer in the goitrous population.

Interest in this subject was stimulated by a study of cancer morbidity in ten metropolitan areas of the United States.[6] Thyroid cancer incidence in 6 of these areas was reported for the year 1947 and in the other 4 areas for 1948. Age-adjusted incidence rates per million population were as follows:

Atlanta, Georgia	12	Detroit, Michigan	20
Chicago, Illinois	15	Pittsburgh, Pennsylvania	21
Dallas, Texas	15	Denver, Colorado	23
New Orleans, Louisiana	16	Philadelphia, Pennsylvania	34
Birmingham, Alabama	20	San Francisco, California	46

The so-called goiter areas of Chicago and Detroit were found to have the same incidence of thyroid cancer as the nongoitrous regions of Birmingham and Dallas.

A brief note concerning the etiology and prevention of goiter, and the clinical and experimental evidence relating goiter to thyroid cancer and thyrotoxicosis will be presented to help the reader interpret the findings and evaluate the conclusions. The geographic distribution and trend of prevalence of goiter in the United States will be considered in relationship to the geographic distribution and trend of mortality attributed to thyroid cancer and to thyrotoxicosis in an

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effort to determine whether these relationships are consistent with the hypothesis that goiter plays a role in the pathogenesis of thyroid cancer and of thyrotoxicosis.

ETIOLOGY AND PREVENTION OF GOITER

According to Rundle,[7] "Any goiter which is neither inflammatory nor malignant and not associated with toxic features may be considered as simple; but it must be admitted that there are objections to such a definition." Taylor[8] has traced the evolution of nodular goiter and feels that the earliest change is diffuse hyperplasia. The diffuse goiter may regress completely, but there is a tendency for it to progress through periods of hyperplasia and involution to the stage of nodularity. The degree of degeneration of the thyroid increases with the severity of iodine deprivation and the age of the patient. When iodine deficiency is not severe, small smooth goiters predominate in children, while nodular and cystic goiters occur more frequently in adults. When severe iodine deficiency is evident, nodular and cystic goiters occur more frequently in infancy and early childhood.

Goiter is usually divided into endemic and sporadic types, although the same fundamental etiological agents are responsible for both. Endemic goiter occurs in specific geographic regions and is considered to be due to iodine deficiency in soil, water, and food.[9-14] Sporadic goiter occurs in regions where iodine is considered to be at least adequate in supply and is probably the result of a relative iodine deficiency produced by some goitrogenic agent.

The most important goitrogens are: physiologic stress; foods such as cabbage, turnips, Brussels sprouts[15,16]; and medicinal agents such as cyanates[17,18] and the thiourea preparations.[19] The combination of increased physiologic need and limited iodine supply is probably the most universal goitrogenic agent. Increased demands are made on the thyroid during periods of puberty, menstruation, pregnancy and lactation, emotional stress, trauma, surgery, and diseases.[20,21] Regularly recurring periodic hormone changes are at least partly responsible for the increased frequency of goiter in women.

TABLE I. GOITER PREVALENCE AMONG SCHOOL CHILDREN IN SELECTED AREAS, BEFORE AND AFTER INTRODUCTION OF IODIZED SALT

AREA AND USE OF IODIZED SALT	PER CENT OF SCHOOL CHILDREN WITH GOITER	
	BEFORE USE OF IODIZED SALT, 1924	AFTER USE OF IODIZED SALT, 1936
State of Michigan*	38.6	8.2
Regular use of iodized salt	——	2.9
Non-use of iodized salt	——	19.3
Cleveland, Ohio†	31.0	18.5
Regular use of iodized salt	——	7.7
Non-use of iodized salt	——	30.7
Lausanne, Switzerland†	57.0	1.0 (1937)

*Data from Kimball.[23]
†Data from Eggenberger and Messerli.[24]

In 1852 Chatin pointed out that goiter was more common in regions where soil and water are low in iodine.[22] Large-scale attempts to prevent human goiter were not successful until 1917, when Kimball and Marine began experimental administration of sodium iodide to girls attending public schools in Akron, Ohio. Impressive evidence of the value of iodized salt in the prevention of goiter, collected by Kimball[23] and Eggenberger and Messerli[24] is presented in Table I.

THE RELATION OF CANCER OF THE THYROID TO GOITER

Clinical Evidence.—There is considerable evidence, both clinical and experimental, that nodular goiter may predispose to thyroid cancer. Wegelin[25] in 1928 reported on the frequency of cancer of the thyroid found at autopsy and showed that it varied from a high of 1.04 per cent in Berne, Switzerland, a highly goitrous area, to a low of 0.09 per cent in Berlin, Germany, a nongoitrous region. Wespi and Eggenberger[26] recorded the death rates from thyroid cancer in Canton Zurich, Switzerland, and showed that from 1906 to 1945 there had been a decrease in goiter and in deaths from thyroid cancer which the authors felt was associated with the increased use of iodine for goiter prophylaxis.

Wegelin[25] reported from the Berne Pathologic Institute in 1928 that "cystadenoma papilliferum malignum has not been found to be related to simple goiter or to adenoma. This rare tumor is no more frequent in goiter districts than elsewhere. It appears in most cases to be derived from isolated branchiogenic 'rests' especially when it occupies the lateral cervical region." Thalmann[27] has recently reported on the frequency of malignant goiter at the same institute during the period 1910 to 1950. He stated that since the introduction of prophylactic iodine there had been a reduction in benign nodular goiter and in thyroid adenocarcinoma and sarcoma. Because an increase in malignant papillary tumors of the thyroid and macrocellular adenomas occurred, however, the frequency of total thyroid cancers did not decrease. Figures from the Mayo Clinic[28,29] indicate that in recent years there has been an increased frequency of papillary carcinoma but that the frequencies of malignant adenoma and anaplastic carcinoma of the thyroid have decreased.

Data collected by the National Cancer Institute in the 1947-1948 survey of cancer morbidity in ten metropolitan areas of the United States indicate that the incidence rate of papillary carcinoma of the thyroid changes very little with advancing age.[30] The incidence of other histologic types of thyroid cancer increases progressively with age. These observations lend themselves well to the hypothesis that follicular and anaplastic carcinoma of the thyroid are related to adenomatous goiter and have decreased because of widespread goiter prophylaxis. The increase in papillary carcinoma is less easily explained.

According to Willis,[31] "Papillary adenomas cannot be distinguished from papillary carcinomas. . . . Demonstrable invasion of small veins in an 'adenoma' or its capsule, if certain, places it in the malignant class. As Erhardt, Erdheim, Graham, Warren, and Dunhill have all shown, later recurrence or metastasis from such tumours is frequent, however 'benign' their structure." This suggests that some tumors of the thyroid that were formerly thought to be benign are now regarded as malignant. Perhaps most of the apparent increase

in papillary carcinoma of the thyroid merely reflects improved recognition of thyroid tumors and a change in criteria used for their classification.

Experimental Evidence.—Experimental evidence indicates that iodine deficiency or various goitrogens may cause a progression of changes in the thyroid gland from diffuse hyperplasia, to nodular hyperplasia, to benign tumor, to thyroid cancer. In 1925 Ivy[32] found goiter in 89 per cent of 2,000 dogs autopsied in Chicago. Of these, 1.6 per cent contained metastasizing neoplasms. Two years later, following the introduction of iodized salt, both types of lesions had disappeared. The occurrence of goiter in rat colonies in areas where goiter is endemic was first observed by Langhans and Wegelin[33] in 1919. Later, the presence of malignant changes was found. Goiter rapidly disappeared after the addition of iodine to the drinking water. The great volume of work done with various foods and chemicals as goitrogens has been well summarized by Bielschowsky.[34] He shows convincingly that when thyroxin deficiency is produced by some goitrogen, the thyroid is overstimulated by the pituitary. The resulting hyperplasia progresses to formation of malignant tumors in a significant number of animals.

THE RELATION OF THYROTOXICOSIS TO GOITER

Clinical Evidence.—Substances now known to contain iodine, such as seaweed and burnt sponge, are said to have been used by the Chinese for treatment of goiter fifteen centuries B.C. Iodine had been tried sporadically in France and Switzerland before 1900. Breuer,[35] in 1900, described hyperthyroidism occurring in goitrous patients treated with iodine. This clinical observation led Kocher[36] and others to discourage the use of iodine in the treatment of nodular goiter because of the possibility of inducing thyrotoxicosis.

By 1924, animal experiments and clinical trials had proved the value of iodine in goiter prevention. In spite of the predictions of induced hyperthyroidism, iodized salt was introduced to the public for general use at that time. In 1931, Plummer[37] reported an epidemic of exophthalmic goiter and of adenomatous goiter with hyperthyroidism as indicated by the increasing numbers of patients seen at the Mayo Clinic. He stated that the onset of the epidemic was coincident with the introduction of iodized salt. It reached a peak in 1926 and 1927 and then gradually fell to the 1923 level. He felt that the evidence at that time did not warrant an attack on the use of iodized salt.

McClure,[38] in 1934, reported on thyroid surgery in Detroit as affected by the use of iodized salt. He noted a marked increase in the number of thyroidectomies done for thyrotoxicosis in adenomatous goiter. There was a concomitant rise in the death rate from goiter reported by the local Board of Health. This increase was coincident with the widespread use of iodized salt and seemed to reach a peak in 1928 and 1929. By 1933 it had returned to the level of the period preceding the widespread use of iodized salt. His conclusions were that iodized salt had caused an initial increase in morbidity and mortality from thyrotoxicosis induced in adenomatous goiter. By 1938, however, the use of iodized salt had reduced the prevalence of goiter and the frequency of thyrotoxicosis had also decreased.

Some authors have questioned the occurrence of iodine hyperthyroidism. Kimball[39] reported a resurvey in 1928 which showed that, among adults with

long-standing goiter who had used iodized salt, 4.1 per cent had developed toxic goiter. Of those who had purposely avoided iodized salt, 55 per cent had developed toxic symptoms.

Marine[40] reported that, in the 10 years following a large-scale goiter prevention experiment in Akron in 1919, many kinds of iodine medication, including candies, tablets, and chewing gum, were widely used. This was accompanied by a rapid rise in the admission rates of most hospitals and clinics in the Great Lakes goiter area for what was designated as "adenomatous goiter with hyperthyroidism." Marine believes that this was the result of abuse of iodine medication in cases of adenomatous goiter. Several years later, as the number of new cases of adenomatous goiter was reduced by prevention, there was less opportunity for induction of hyperthyroidism through excessive iodine administration.

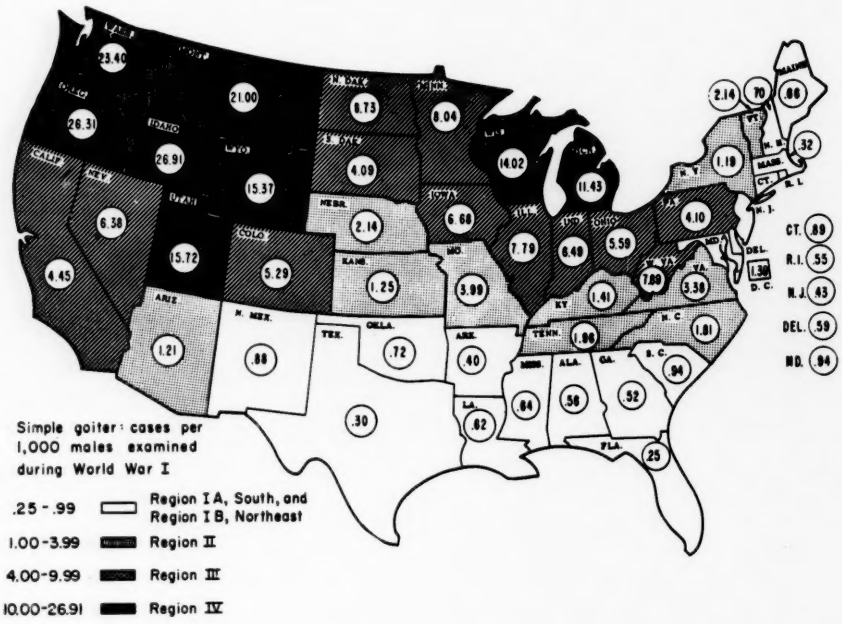

Fig. 1.—Prevalence rates of simple goiter among males examined for military service during World War I: United States by states, 1917-1918.

Experimental Evidence.—Iodine-induced thyrotoxicosis in animals with adenomatous goiter has been demonstrated. The best-known reports are those of Webster and Chesney,[41] who studied rabbits in which goiters had been induced by a diet of cabbage. The administration of excessive doses of iodine to these rabbits caused fatal and nonfatal hyperthyroidism. They concluded that the intensity of the thyrotoxicosis depended more on the size of the goiter than on the amount of iodine administered. Other pertinent experimental evidence has already been mentioned in the discussion of goiter and cancer of the thyroid.

DEFINITION OF GOITER REGIONS IN THE UNITED STATES

The existence of a goiter belt in the Great Lakes area has been generally recognized for many years. However, the first approximate conception of the nationwide distribution of goiter became available with the compilation of draft statistics of World War I.[42] The draft examinations during World War II[43] offer an interesting comparison and demonstrate the changes following the use of iodized salt for 20 years. Draft examinations have certain unavoidable limitations which affect the accuracy of the findings. First, the subjects were young men in whom goiter is less prevalent than in the general population. Second, there was variation in degree of skill and experience among examining physicians in the diagnosis of thyroid disorders. We are willing to accept these figures as the best available, however, because they represent a relatively good sample of a well-defined population and, in general, agree with the data of local and regional surveys.[9-14,44,45]

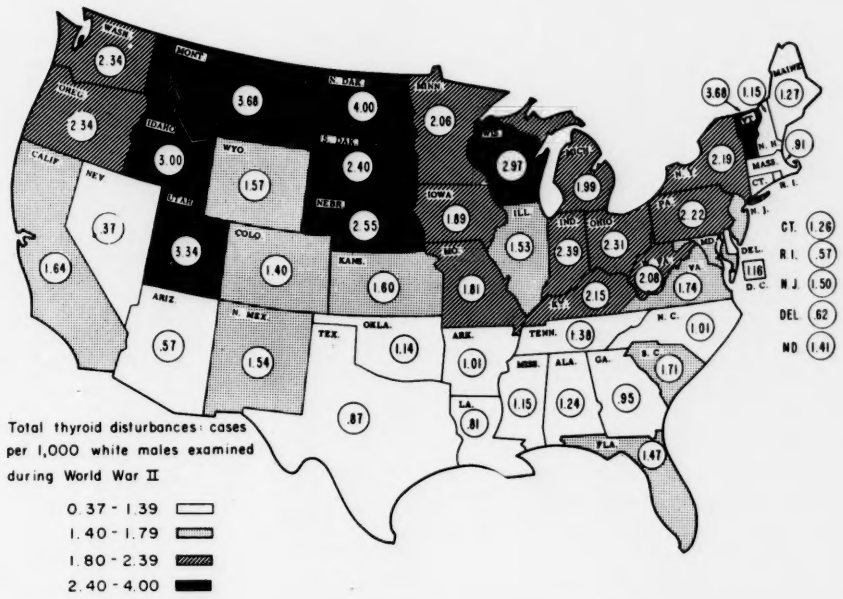

Fig. 2.—Prevalence rates of total thyroid disturbances among white male Selective Service Registrants during World War II: United States by states, 1940-1944.

Among about two and a half million men examined during World War I, the simple goiter prevalence rate was 4.4 per 1,000. Thirty-one per cent of the men with simple goiter were rejected because their necks were too large to permit wearing the military collar. Fig. 1 shows the prevalence of simple goiter in each state. The states were grouped into four regions, designated I to IV in order of increasing goiter prevalence. Region I, the area of lowest prevalence, contains two widely separated groups of states. Therefore it was subdivided into Region IA, Southern States, and Region IB, Northeastern States. Goiter occurs most

frequently in Region IV, which consists of states in the Great Lakes and northwestern areas.

In World War II the occurrence of simple goiter was so rare that it was not separately identified in published reports. It was included under the heading, "total thyroid disturbances," comprising hyper- and hypothyroidism, toxic and nontoxic goiter, myxedema and cretinism, and thyroidectomy. Among 2,396,152 white Selective Service examinees (a 20 per cent sample of all examinees), 4,253 cases of goiter and other thyroid disturbances were noted—a prevalence of only 1.8 per 1,000. Prevalence rates for each state are shown in Fig. 2. Though not directly comparable, the geographic distribution of total thyroid disturbances during World War II is generally similar to that of simple goiter during World War I (Fig. 1).

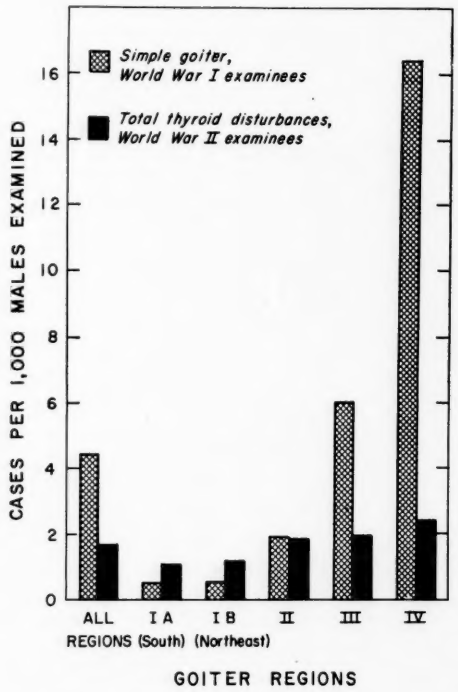

Fig. 3.—Prevalence rates of simple goiter among World War I male examinees and of total thyroid disturbances among World War II white male examinees: United States and regions. (For definition of regions, see Fig. 1.)

The coefficient of correlation between the prevalence rates shown in Figs. 1 and 2 is 0.58. It is significantly different from zero at the .001 level of statistical significance. Fig. 3 shows the World War I simple goiter and World War II total thyroid disturbances prevalence rates for the United States and each goiter region. The regions retained their relative positions, but differences among the regions were much smaller during World War II. The range of regional prevalence rates per 1,000 men examined for endemic goiter during World War I was from

0.53 to 16.43. In contrast, the World War II range for total thyroid disturbances was from 1.09 to 2.45 per 1,000.

The reduction in goiter prevalence between World War I and World War II seems to be due to the general use of iodized salt and the relatively wider distribution of fresh fruits and vegetables available at all times of the year. Although there has been a marked decrease in clinical goiter, there is pathologic evidence that goiter is still widely distributed and remains relatively more prevalent in the endemic goiter areas. Rice,[46] in 1932, studied the frequency of nodular thyroids found at autopsy in Minnesota. Nodules were rare before age 20, but were present in almost 100 per cent of autopsied cases by age 75. Mortensen and associates[47] in 1955, reported from autopsy studies of clinically normal thyroids a frequency of 40.7 per cent nodular changes in people who had lived in the goiter belt and in 18.3 per cent of people from nongoitrous areas. Vander and co-workers[48] reported on 5,234 people chosen by random selection in the nongoitrous region of Framingham, Mass. Physical examination disclosed the presence of

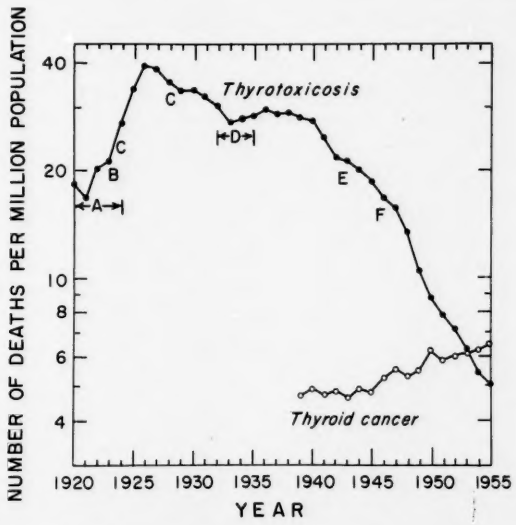

Fig. 4.—Crude mortality rates for thyrotoxicosis, 1920-1955, and for cancer of the thyroid, 1939-1955: Death Registration States, 1920-1932, and United States, 1933-1955.
A, 1920-1924: Iodine used in some areas of the United States for prevention of goiter.
B, 1923: Large doses of iodine advocated in preparing patients with toxic goiter for surgery.
C, 1924 and 1928: Widespread campaigns advocating use of iodized salt for prevention of goiter.
D, 1932-1935: Decrease in use of iodized salt during economic depression.
E, 1943: Introduction of thiourea for the treatment of thyrotoxicosis.
F, 1946: Introduction of I^{131} for the treatment of thyrotoxicosis.

nodules of the thyroid gland in 3.0 per cent of the surveyed population. The prevalence of nodules among females was 5 times as great as among males. Thus it appears that, although goiter has been reduced in frequency and severity, it is still quite common and still has an apparent pattern of geographic distribution.

The persistence of goiter after almost 30 years of prophylactic iodine is partly explained by the information from the Salt Manufacturers Association[49]

that at present only about 50 per cent of the salt sold for human consumption is iodized.

TRENDS IN THYROID CANCER AND MORTALITY FROM THYROTOXICOSIS

Crude mortality rates for both thyrotoxicosis and thyroid cancer[50-52] are shown in Fig. 4. Data for thyrotoxicosis are available since 1920 but for thyroid cancer only since 1939. The death rate for thyroid cancer has changed very little during the years available for study. About half of the increase from 4.7 per million population in 1939 to 6.5 per million in 1955 is attributable to changes in the age distribution of the population. In contrast, age-adjusted thyrotoxicosis mortality rates indicate a sharper downward trend than is suggested by crude rates. (Age-adjusted mortality rates for selected years are presented in Table II and Fig. 7.)

Crude thyrotoxicosis mortality rates increased from 18 to 40 per million population during the years 1920 to 1926; declined irregularly to 28 in 1940 and then followed a steadily downward course to 5 per million in 1955. It is interesting

TABLE II. ADJUSTED AVERAGE ANNUAL MORTALITY RATES* FOR THYROTOXICOSIS AND FOR CANCER OF THE THYROID, 1929-1931,† 1939-1941, AND 1949-1951; PREVALENCE OF SIMPLE GOITER AMONG MEN EXAMINED FOR MILITARY SERVICE DURING WORLD WAR I, AND PREVALENCE OF TOTAL THYROID DISTURBANCES AMONG WHITE MEN EXAMINED FOR MILITARY SERVICE DURING WORLD WAR II: UNITED STATES AND GOITER REGIONS‡

DISEASE AND TIME PERIOD	UNITED STATES	GOITER REGIONS AS DEFINED IN FIG. 1				
		IA	IB	II	III	IV
Average Annual Mortality per Million Population.—						
Thyrotoxicosis						
1929–1931	46.2†	15.1†	22.4	36.9	54.4	79.3
1939–1941	29.8	15.1	20.8	27.4	37.7	45.1
1949–1951	9.1	7.5	6.3	8.4	10.5	11.8
Thyroid cancer						
1939–1941	5.3	2.8	6.4	5.3	5.9	6.1
1949–1951	5.9	4.2	6.3	5.9	6.1	6.7
Prevalence per 1,000 Men Examined for Military Duty.—						
Simple goiter						
World War I	4.43	.53	.55	1.93	6.05	16.43
Total thyroid disturbances (white males)						
World War II	1.77	1.09	1.20	1.88	2.01	2.45

*Adjusted by the indirect method for differences in age, race, and sex, with the use of United States rates for 1949-1951 as standard.

†Thyrotoxicosis mortality rates for 1929-1931 do not include Texas because Texas was not among the Death Registration States at that time. Deaths attributed to cancer of the thyroid are not identifiable for the United States or any state in the annual Mortality Statistics[50] reports for 1929-1931, or for any other year prior to 1939.

‡For definition of goiter regions, see Fig. 1.

to attempt to correlate these changes in mortality with the use of iodine as a preventive and therapeutic measure, and with the improvements in medical and surgical management of thyrotoxicosis.

From 1919 to 1924 iodine was used in only a few places for goiter prevention. The dramatic results of these local trials led to the general use of a standard iodized salt. Vigorous campaigns to publicize the benefits of iodized salt were conducted in 1924 and again in 1928.

In 1923, Plummer[53] advocated the use of large doses of iodine in preparing the patient with toxic goiter for operation. In spite of improved preoperative preparation the mortality from thyrotoxicosis rose from 21 per million population in 1923 to 40 per million population in 1926. It is difficult to escape the conclusion that this increased mortality was due to thyrotoxicosis induced in long-standing goiter by the excessive use of iodine.

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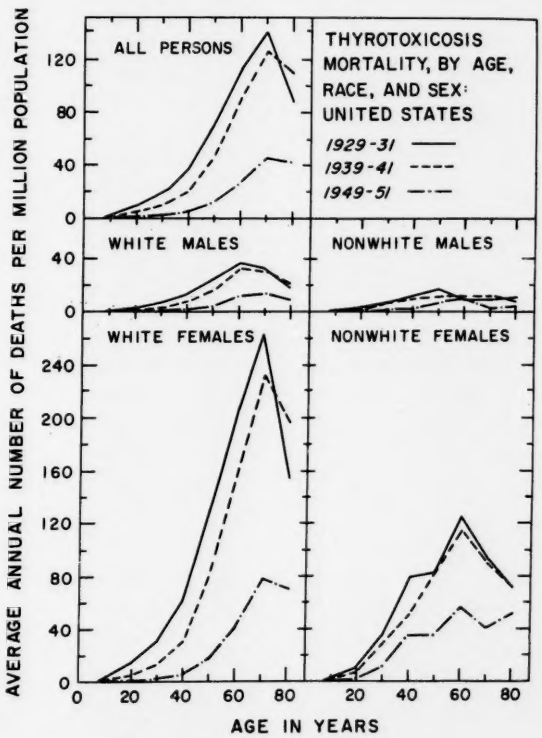

Fig. 5.—Average annual mortality rates for thyrotoxicosis, by age, race, and sex: Death Registration States, 1929-1931, and United States, 1939-1941 and 1949-1951.

The decrease in thyrotoxicosis death rates after 1926 seems to parallel the reduction in goiter prevalence resulting from the use of iodized salt, as suggested in Table I. The slight rise in rates from 27 to 30 per million population during the period 1933 to 1936 might be explained by the documented observation[39] that during the depression years 1932 to 1935 a large number of people were using

non-iodized salt with a concomitant increase in endemic goiter. The rapid fall in thyrotoxicosis mortality since 1940 is probably in part due to improved therapy and in part to goiter prevention by the use of iodized salt.

Average annual thyrotoxicosis mortality rates by age, race, and sex for the United States during the periods 1929-1931, 1939-1941, and 1949-1951, are shown in Fig. 5. It is apparent that there has been a marked decrease in deaths ascribed to thyrotoxicosis, particularly during the latter decade. Both white and nonwhite female death rates are about five times as high as corresponding male rates. This is in agreement with the clinical observation that diseases of the thyroid are about five times as frequent in women. In general, nonwhite rates exceed white rates for both sexes at ages under 45 while the reverse holds true for ages 55 and over. The difference between white and nonwhite rates is much greater for 1929-1931 than for 1949-1951.

As pointed out by Clements[54] on the basis of cohort analysis, there has been a reduction in the thyrotoxicosis mortality rate in Australia in each succeeding cohort. This also occurred in the United States, as may be seen if cohort mortality lines are added to Fig. 5 between appropriate points. Clements states that, if this improvement in mortality were due to newer methods of treatment alone, all age groups would have shown a uniform degree of change. Since the more recent cohorts, or younger individuals, have had a preferential improvement in mortality, Clements believes that the use of prophylactic iodine is largely responsible.

Our data (Table II) concerning regional variation in thyrotoxicosis mortality also suggest that goiter prophylaxis has been the primary factor in reducing mortality. Since therapy is fairly uniform throughout the country, improvements in therapy would not explain the preferential improvements in mortality as seen in the more goitrous regions of the United States.

Thyroid cancer mortality rates by age, race, and sex for the United States in 1939-1941 and 1949-1951 are shown in Fig. 6. There has been a moderate increase in death rates at age 65 and over. The difference between white and nonwhite rates was considerably greater in 1939-1941 than in 1949-1951. Though not shown in Fig. 6, in 1949-1951 the ratio of female to male rates for all ages combined was about 2.0 for whites and 1.5 for nonwhites. Also, white rates exceeded nonwhite rates by about 18 per cent among males and 63 per cent among females.

CORRELATION OF ENDEMIC GOITER PREVALENCE WITH MORTALITY RATES FOR THYROID CANCER AND FOR THYROTOXICOSIS

If endemic goiter is involved in the pathogenesis of thyrotoxicosis or of cancer of the thyroid, one would expect: (1) that mortality rates from the latter two diseases would be relatively high in geographic areas of high goiter prevalence; (2) that during the last three decades, as a consequence of reduced endemic goiter prevalence, mortality attributed to thyrotoxicosis or thyroid cancer would decline (assuming constancy of other etiological factors); and (3) that this decline would be greatest in geographic areas in which the prevalence of endemic goiter had been most markedly reduced.

Thyrotoxicosis and thyroid cancer mortality rates, adjusted for differences in age, race, and sex composition of the population, are shown in Table II and Fig. 7 for the United States and for the goiter regions as defined in Fig. 1. For thyrotoxicosis, average annual death rates per million population are given for the periods 1929-1931, 1939-1941, and 1949-1951. Corresponding rates for cancer of the thyroid are presented only for the latter two periods because earlier data are not available.

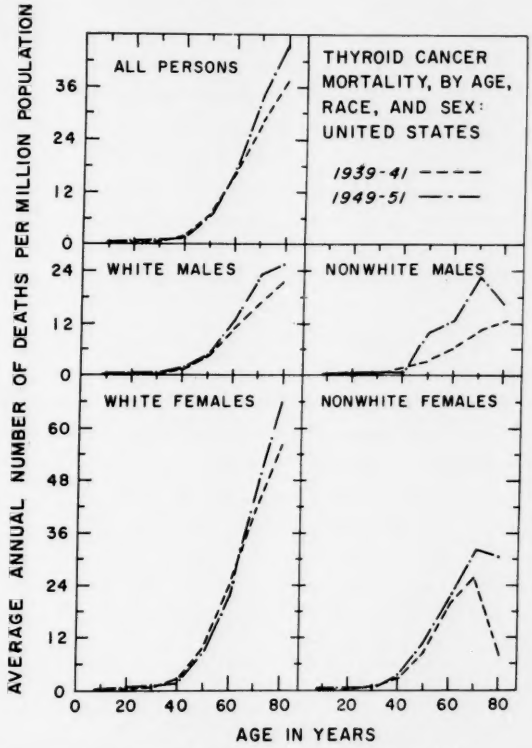

Fig. 6.—Average annual mortality rates for cancer of the thyroid, by age, race, and sex: United States, 1939-1941 and 1949-1951.

For the entire United States, the adjusted thyrotoxicosis mortality rate for the 3 years 1949-1951 was only about one-fifth as great as the rate for 1929-1931. Mortality rates in each of the regions also declined. The reduction was greatest in Region IV, the region of highest goiter prevalence, and least in Regions IA and IB, the least goitrous regions. Differences among regions were much smaller in 1949-1951 than they were 10 and 20 years earlier. With the minor exception of Regions IA and IB (which exchanged rank orders in 1949-1951), regional thyrotoxicosis mortality rank orders remained constant in each of the 3 time periods and conformed exactly to regional rank orders for simple goiter during World War I and for total thyroid disturbances during World War II.

Adjusted thyroid cancer mortality rates for the United States changed very little from 1939-1941 to 1949-1951. There was some increase in every region other

than IB, in which the rate remained essentially the same. Regional rank orders were different in these 2 time periods and in neither case did they resemble the rank orders for simple goiter or for total thyroid disturbances during World Wars I and II, respectively.

If endemic goiter is involved in the etiology of cancer of the thyroid, there could be a latent period of several decades between onset of goiter and appearance of cancer. It is reasonable to expect, however, that there would be at least some reduction in thyroid cancer mortality in the United States as a whole within 30 years, if such an effect is to occur at all. Actually, the trend of mortality attributed to cancer of the thyroid is slightly upward. The possibility of a latent period of 40 or more years cannot be excluded on the basis of data now available.

The 3 coefficients of correlation between regional thyrotoxicosis mortality in each of the 3 time periods with regional prevalence of simple goiter, World War I, ranged from 0.90 to 0.95. They are significantly different from zero (null hypothesis), p ranging from 0.013 to 0.041. Similar comparison of thyrotoxicosis mortality with prevalence of total thyroid disburbances, World War II, yielded coefficients of correlation from 0.93 to 0.97 and corresponding p values from 0.009 to 0.026.

In contrast, coefficients of correlation between regional thyroid cancer mortality and the two sets of regional prevalence rates ranged from 0.42 to 0.68 but were not significantly different from zero (p values from 0.20 to 0.49).

Correlation between regional rates does not make maximum use of available information about geographic variation. Therefore coefficients of correlation (r) based on rates in each state were also computed. These coefficients and the statistical significance (p) of the difference between each and zero are shown in Table III.

For thyrotoxicosis, all r and p values are lower than those that were based on regional rates. Thus the magnitude of correlation coefficients for the 6 com-

TABLE III. CORRELATION OF AVERAGE ANNUAL MORTALITY RATES FOR THYROTOXICOSIS AND FOR CANCER OF THE THYROID FOR EACH STATE, 1929-1931, 1939-1941, AND 1949-1951, WITH PREVALENCE RATES FOR SIMPLE GOITER, WORLD WAR I, AND FOR TOTAL THYROID DISTURBANCES, WORLD WAR II

TIME PERIOD	THYROTOXICOSIS MORTALITY, BY STATES, CORRELATED WITH:				THYROID CANCER MORTALITY, BY STATES, CORRELATED WITH:			
	SIMPLE GOITER PREVALENCE, WORLD WAR I		TOTAL THYROID DISTURBANCES PREVALENCE, WORLD WAR II		SIMPLE GOITER PREVALENCE, WORLD WAR I		TOTAL THYROID DISTURBANCES PREVALENCE, WORLD WAR II	
	r	p	r	p	r	p	r	p
1929–1931	.64	< .001	.53	< .001	—	—	—	—
1939–1941	.59	< .001	.56	< .001	.23	.11	.22	.14
1949–1951	.36	.012	.52	< .001	.30	.040	.12	.42

parisons is smaller than suggested by regional comparisons, but their statistical significance is very much higher; p is less than 0.001 in 5 instances and is 0.012 in the remaining case. These observations clearly support the hypothesis that endemic goiter is an important factor in the pathogenesis of thyrotoxicosis.

For thyroid cancer, r and p values are also lower than corresponding values based on regional correlation. In only one of the 4 comparisons is r statistically significant at the 4 per cent level of significance. In this case r is 0.30 and p is 0.040. The coefficient of determination, r^2, is the proportion of total variance explainable by the independent variable. Thus, if the correlation between thyroid cancer mortality during 1949-1951 and simple goiter prevalence during World

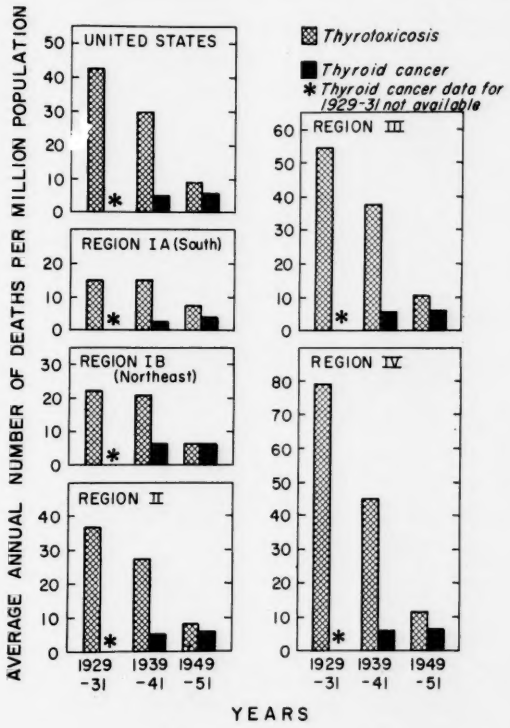

Fig. 7.—Adjusted average annual mortality rates for thyrotoxicosis and for cancer of the thyroid: United States and regions, 1929-1931, 1939-1941, and 1949-1951. (For further explanation, see footnotes of Table II.)

War I is regarded as statistically significant, only 9 per cent of the variance is explainable on this basis. These comparisons of geographic variation in thyroid cancer mortality with indexes of goiter prevalence do not provide convincing evidence for the existence of an association between these two diseases.

Clements[54] in Australia and Saxen and Saxen[55] in Finland were also unable to demonstrate a relationship between thyroid cancer mortality and goiter prevalence.

SUMMARY

Some clinical evidence suggests that goiter predisposes to cancer of the thyroid as well as to thyrotoxicosis. A high frequency of pre-existing goiter has been reported in patients with thyroid cancer and the possibility of thyroid cancer must always be considered in patients with nodular goiter. Studies which are restricted to selected patients with cancer of the thyroid cannot be expected to indicate whether persons with goiter are more likely than others to develop thyroid cancer.

Experimental evidence indicates that in animals iodine deficiency or goitrogens may cause progressive changes in the thyroid gland from diffuse to nodular hyperplasia to benign tumor and, sometimes, to malignant neoplasm.

Simple goiter is largely a preventable disease and there has been an impressive decline in its frequency since the introduction of iodized salt. Medical examinations of candidates for military service during World Wars I and II reflect this decrease. They also indicate that there are geographic differences in goiter prevalence which, though much less marked, were still present after two decades during which iodized salt was generally available.

The trend and geographic variation of goiter prevalence were compared with the trends and geographic patterns of mortality attributed to thyrotoxicosis and to thyroid cancer. The comparison of goiter with thyrotoxicosis indicates a highly significant correlation that strongly supports the hypothesis that endemic goiter is an important factor in the pathogenesis of thyrotoxicosis. In contrast, the comparison of goiter and thyroid cancer does not provide convincing evidence for the existence of an association between these two diseases.

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Vol.
19

Vol. 13
1961

A SAMPLING STUDY OF BLOOD PRESSURE LEVELS IN WHITE AND NEGRO RESIDENTS OF NASSAU, BAHAMAS

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MANY factors have been tentatively identified as correlates of blood pressure. These include age, sex, race, body build or obesity, dietary components, particularly sodium, and genetic susceptibility. While there is general agreement that each of these factors plays some role, the exact quantitative nature of this role is a subject of controversy.

Some of the disagreement present in the literature on blood pressure is no doubt due to the differing composition of the groups that have been studied and to preoccupation with study of a single factor, all other factors being neglected or ignored. For a discussion of some of the factors influencing blood pressure, see Pickering.[7]

The population of the Bahama Islands offers a unique opportunity for simultaneous study of several of the important factors related to blood pressure. Residents of these islands are primarily Negro, although about 20 per cent of the population is Caucasian. This permits the simultaneous study of the factors of race, age, and sex. Another interesting feature of the Bahamas is the known high sodium content of the water supply. The importance of salt intake in the pathogenesis of hypertension is controversial, but no good data are available in regard to population differences in salt intake compared to distributions of blood pressure.

There have been many studies of the distribution of blood pressure in human populations. In general, these studies have been concerned with special groups of people, such as insurance policy holders, industrial workers, and clinic outpatients and inpatients. Each of these groups might possibly differ in blood pressure distribution, thus making it a potentially poor representative of a large general

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population. On the other hand, there have been several studies of large populations which do not suffer from this particular difficulty. Some investigators have studied communities, whereas others have studied scientifically designed samples of a community. Some of these efforts, however, have suffered from the failure to get observations from many of the people designated for study, again inviting statistical criticism.

It would be extremely difficult to sample adequately the entire population of the Bahama Islands. The population is scattered among a great number of islands, over a large geographic area. The Island of New Providence is the cultural and geographic center of the island group, however, and contains the only relatively large city in the islands, the city of Nassau. Thus, Nassau was selected as the site of the study because it is centrally located in the island group, contains a concentration of population, and probably represents a melting pot of the people of the entire colony.

METHODS

Selection of the Sample.—The sample of residents of the city of Nassau selected for this study is technically known as a stratified one-stage cluster sample. The basic sampling unit consisted of a segment of approximately 40 dwelling units, usually consisting of a city block, or part of a city block. In a preliminary canvass of the population of the city of Nassau, these sampling units were stratified, or divided into groups on the basis of geographic area, racial composition of the residents, and a rough index of socioeconomic status. Ten Negro strata, containing 17 or 18 sampling units each, were so identified. An additional stratum containing a racially mixed population and consisting of 16 sampling units was defined. A twelfth stratum, consisting mainly of white residents and containing 12 sampling units, completed the stratification of the population. Two sampling units were selected at random from each of the Negro strata and from the mixed stratum. Because of the relatively small number of white residents, and because of the need to secure a racial comparison in the study, 4 sampling units were selected at random from the white stratum.

The considerations leading to the choice of this size for the sample include the physical and financial resources available to the study, and the desire to analyze the data separately for the various age, sex, and race groups.

The selected sample was studied over a 6-week period, and data were collected on 92 per cent of the individuals falling into the sample. This yielded 1,250 Negro women, 990 Negro men, 362 white women, and 325 white men. Some families of obviously mixed racial stock were studied but, unfortunately, were too few in number for analysis.

Interview and Examination Procedure.—This study was designed to permit examinations to be carried out in the subject's home. Home examinations promised more complete coverage of families. Furthermore, a casual blood pressure taken at home probably provides a reasonably accurate measure of the blood pressure a person "lives with" when not subjected to stress, although it is perhaps affected to some degree by the presence of a strange person in the home. Examinations were, of necessity, performed when the individual subject could be found

at home. This frequently involved several callbacks before an entire family could be examined. For this reason, variation in blood pressure due to time of day, elapsed time since last meal, fatigue, etc., could not be compensated for by standardization. Most of the people were seen between 2 and 9 P.M., although some were seen in the morning.

Examinations were done in almost equal numbers by one physician (senior author) and 4 senior medical students from the University of Michigan. The interview itself was standardized so that information was gathered in a systematic manner. The medical data were collected in the following order: (1) arm girth measurement, (2) first casual blood pressure reading, (3) first pulse rate, (4) height measurement, (5) weight measurement, (6) second blood pressure, (7) second pulse rate.

Blood pressure readings were taken from the left arm, with the subject in the sitting position. In the blood pressure determinations, both fourth phase diastolic (muffling) and fifth phase diastolic (disappearance) were recorded. Pulse rates, timed for 15 seconds, were taken immediately after blood pressure readings. Height and weight measurements were routinely recorded after the first blood pressure and pulse. The blood pressure cuff was left on the arm, since this sped up the examination procedure, and did not materially affect the recorded weight. Simple bathroom scales, portable in a brief case, were used for recording weight. All the five scales used agreed to within three pounds when checked for accuracy. Height was measured to the nearest half inch, with a firm cloth tape, after the height was marked on a wall, the subject standing without shoes. Arm girth was measured to the nearest quarter inch, at the point of maximum circumference of the upper left arm. This firm cloth tape was felt to be comparable in accuracy to a flexible metal tape.

The total elapsed time between blood pressure measurements was one to two minutes. Sphygmomanometers were of the aneroid type, compared daily for accuracy with a mercury manometer as a standard.

In the course of the actual examination procedure, persons were told either that their blood pressure was normal, borderline high, or high. The criterion used for the most part was diastolic pressure. All subjects with diastolic blood pressure over 110 mm. Hg were referred to their physician or to the Colonial Medical Service. Diastolic pressures between 100 and 110 mm. Hg were called borderline and these persons were advised to consult their physician at a later date. Others were called "normal." Some exceptions to these criteria were made in young people, older persons with extremely wide pulse pressures, and others with suggestive symptoms. All these were also referred to their physicians.

Pretesting and Standardization.—After thorough familiarization with the methods and procedures of examination, all examiners engaged in a field test in order to insure uniformity of information collected, and of examination routine. An area of the city not included in the sample was used in the pretest. The examiners worked in pairs during the pretest, observing each other's technique, until it was felt that all were comparable.

Prior to the collection of any of the actual data presented here, an additional standardization experiment was undertaken for the purpose of estimating inter-

TABLE I. MEANS OF BLOOD PRESSURE READINGS IN AGE, SEX, AND RACE GROUPS, WITH STANDARD ERROR OF MEAN—NASSAU, 1958

MALES				FEMALES			
AGE	MEAN	STANDARD ERROR	NO. IN GROUP	AGE	MEAN	STANDARD ERROR	NO. IN GROUP
Systolic Blood Pressure, White Race.—							
6–9	105.90	2.57	45	6–9	104.71	1.69	47
10–14	114.92	2.12	28	10–14	116.90	1.26	36
15–19	128.74	1.19	33	15–19	120.18	1.87	31
20–24	126.75	3.33	34	20–24	122.74	4.97	43
25–29	130.17	2.62	30	25–29	117.91	3.68	39
30–34	124.97	2.55	38	30–34	122.69	2.86	33
35–39	124.91	4.75	22	35–39	120.53	4.74	27
40–44	135.47	2.41	22	40–44	145.15	7.38	25
45–49	128.01	3.52	20	45–49	145.04	2.49	20
50–54	138.73	3.32	14	50–54	145.01	3.90	15
55–59	140.56	8.44	11	55–59	160.70	6.33	16
60+	144.08	6.91	28	60+	156.88	3.51	30
Systolic Blood Pressure, Negro Race.—							
6–9	101.53	1.03	154	6–9	102.56	0.51	166
10–14	109.37	0.62	143	10–14	111.53	1.03	139
15–19	125.11	1.02	139	15–19	118.81	1.23	153
20–24	128.03	1.24	123	20–24	119.65	1.46	170
25–29	132.97	1.83	98	25–29	126.79	2.01	128
30–34	135.89	2.72	58	30–34	132.41	1.48	86
35–39	142.85	5.09	55	35–39	140.26	2.16	109
40–44	142.09	3.17	67	40–44	149.61	4.82	87
45–49	145.30	2.85	67	45–49	152.88	2.04	75
50–54	155.85	4.92	37	50–54	155.99	5.43	46
55–59	144.68	9.34	16	55–59	182.42	5.93	30
60+	168.78	8.80	33	60+	176.41	3.53	61
Diastolic Blood Pressure, Fifth Phase, White Race.—							
6–9	61.31	2.53	45	6–9	66.90	2.38	47
10–14	62.60	2.20	28	10–14	66.96	1.31	36
15–19	71.18	2.18	33	15–19	67.38	0.91	31
20–24	72.65	1.78	34	20–24	73.30	1.88	43
25–29	74.06	4.06	30	25–29	76.55	0.90	39
30–34	77.30	0.92	38	30–34	78.94	2.97	33
35–39	79.39	4.01	22	35–39	77.86	0.92	27
40–44	84.95	1.75	22	40–44	86.38	3.69	25
45–49	79.15	1.32	20	45–49	85.42	2.65	20
50–54	87.75	2.16	14	50–54	86.69	1.83	15
55–59	83.47	2.25	11	55–59	86.25	2.88	16
60+	79.42	2.91	28	60+	81.58	1.16	30
Diastolic Blood Pressure, Fifth Phase, Negro Race.—							
6–9	63.79	0.90	154	6–9	64.71	0.76	166
10–14	66.29	0.55	143	10–14	67.18	1.13	139
15–19	73.56	1.27	139	15–19	71.06	1.19	153
20–24	78.69	1.25	123	20–24	73.81	1.13	170
25–29	82.93	1.38	98	25–29	80.40	1.25	128
30–34	87.75	2.11	58	30–34	84.68	1.11	86
35–39	91.58	2.52	55	35–39	88.18	1.58	109
40–44	91.42	1.72	67	40–44	90.84	2.62	87
45–49	94.41	2.21	67	45–49	92 14	0.92	75
50–54	93.15	1.93	37	50–54	91.56	2.52	46
55–59	86.97	3.99	16	55–59	98.15	1.41	30
60+	90.33	4.45	33	60+	89.74	1.66	61

Vol. 1
196

observer variability in the blood pressure and pulse determinations. Five different subjects were observed by the five field examiners. The examinations were arranged so that the effects of three potential sources of variation could be measured. These were: (1) variation between the subjects, (2) variation between the examiners, and (3) variation due to the order in which the subjects were examined. The examination of each subject by each observer included three successive blood pressure and pulse determinations. Both fourth and fifth phase diastolic pressures were recorded, and pulses were taken with fifteen second readings. Briefly, the results of this standardization experiment were as follows: (1) Variation between subjects was great. (2) Variation due to order of observation was slight or minimally significant statistically. (3) Variation due to observers was not significant for any of the blood pressure variables.

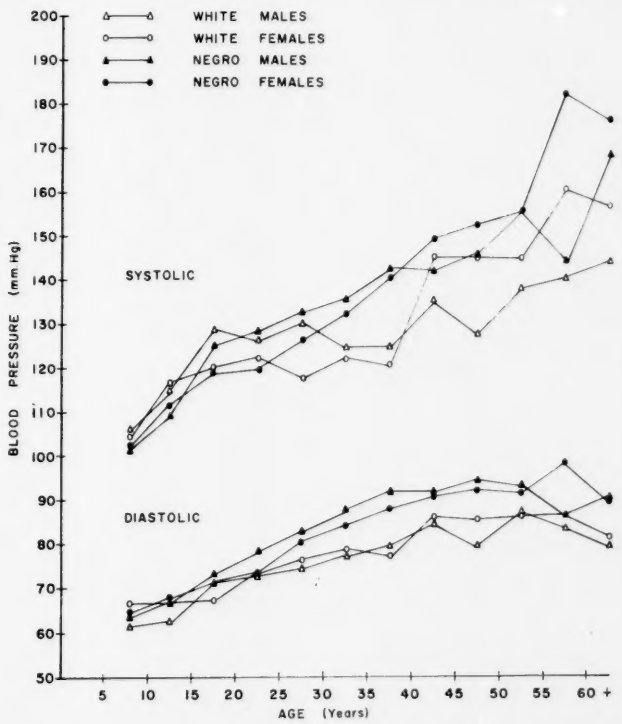

Fig. 1.—The mean systolic and diastolic blood pressure by age, race, and sex—Nassau, 1958.

RESULTS

Table I presents the basic results of the study. The first two sections present the systolic blood pressure for both the white and Negro races, by sex and age. The last two parts present similar results for diastolic (fifth phase). The fourth phase diastolic pressure was recorded routinely but is not presented in this report. Findings were essentially similar to the fifth phase data.

In Fig. I the means of systolic and diastolic (fifth phase) blood pressure are plotted by age, sex, and race. The most striking impression from this figure is the apparent difference in the pattern of progression with age. The nature of this difference is of interest.

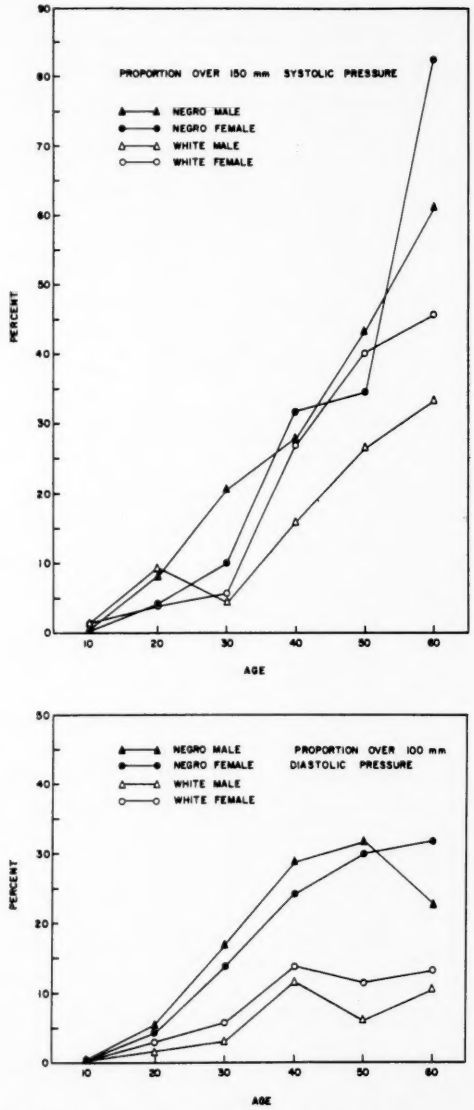

Fig. 2.—The proportion of persons within the age, sex, race group with blood pressure over arbitrary break points within the Negro and white races—Nassau, 1958.

The mean diastolic pressures gradually increase from early childhood to age 55, when they begin to fall slightly. From age 20, the Negro means continue upward fairly steadily, while the means for the white persons remain more nearly

constant. It is also interesting that, after adolescence, there is a very slight but consistently higher mean diastolic pressure for Negro males as compared with Negro females until about age 55. This consistent relationship is not demonstrable in the white race.

In the graph of mean systolic pressures, the increase in the mean by age in the Negro race is seen to be quite regular, proceeding upward in an almost linear fashion. Systolic pressure for the white race seems to rise quite rapidly from childhood to early adulthood (slightly exceeding the Negro means). From this point, however, the white persons show a plateau effect, or a flattening of the progression of pressure with age. At about age 40 (as was seen in the diastolic means) a rather sudden change is seen toward increasing pressures, most marked in the female.

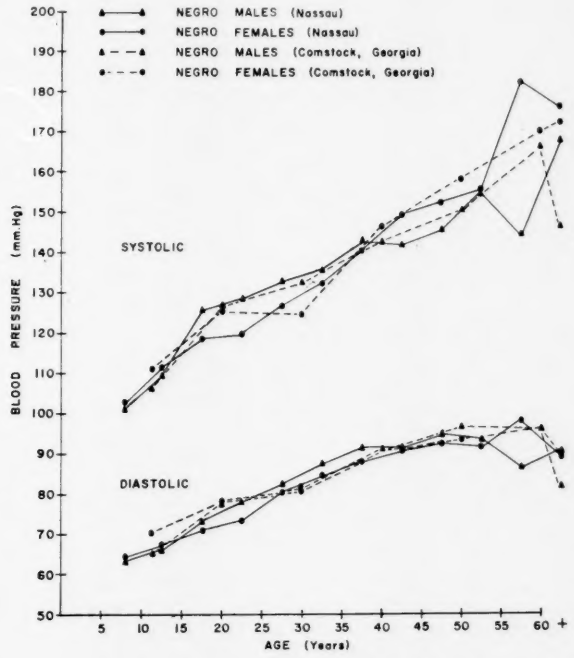

Fig. 3.—The mean systolic and diastolic blood pressure by age in the Negro race—Nassau, 1958, and Georgia.

In regard to the differences by sex, it is seen that there is very little difference between the sexes of either race in childhood. After adult levels are reached (about age 17), the male of both races has consistently higher systolic pressure than the female during the reproductive period. This is somewhat more marked in the white race. In both races this relationship is reversed at almost the same time in life, about age 40. The "crossover" of the lines at the end of the reproductive period suggests that women enjoy a degree of immunity to hypertension during these years which is lost at about the age of menopause. The menopause per se has not previously been shown to have a hypertensive effect, at least no sudden

change not attributable to increase in age. Sex differences in regard to blood pressure have not been adequately explained. The "crossover" of the curves at the age of the menarche and at the menopause, however, suggests a relationship between these physiologic changes and the basic mechanism of blood pressure control.

The pattern in diastolic pressure means does not show this clear-cut sex difference. In fact, the Negro male tends to maintain a very slight but consistently higher mean than the female from adolescence to about age 55.

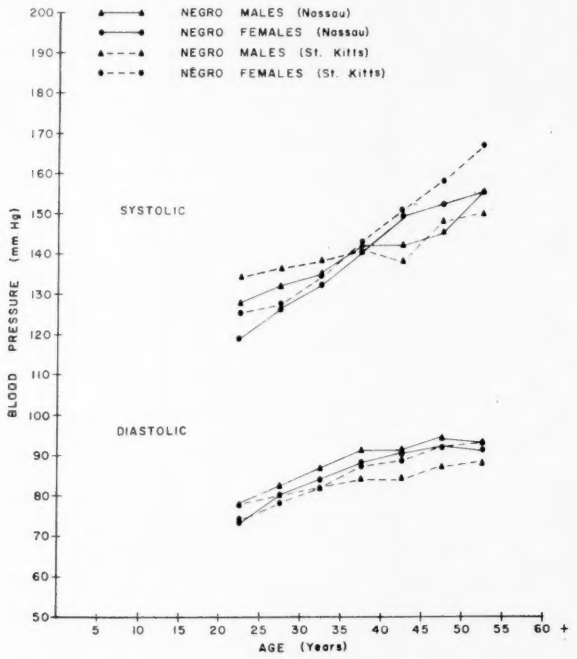

Fig. 4.—The mean systolic and diastolic blood pressure by sex and age in the Negro race—Nassau, 1958, and St. Kitts, Leeward Islands. (Schneckloth and Corcoran.[8])

Fig. 2 describes the racial and sex differences from the point of view of proportions of age-sex-race groups which have blood pressures over specific cut points. In this figure, the cut points are 150 mm. systolic pressure and 100 mm. diastolic pressure. The racial difference is again clearly demonstrable. This graph is generally similar to Fig. 1, although points of crossover in regard to sex are obscured.

Comparison With Other Studies.—External comparisons were made with results in similar racial groups in similar population studies. Comparisons with the data from Comstock,[2] Miall,[5] and Boe[1] lead one to believe that white persons in Nassau are not very different from these other populations in regard to blood pressure. The Negro race in Nassau was compared specifically with studies done among Negroes in Georgia[2] and in St. Kitts (Leeward Islands).[8] Figs. 3 and 4

show the remarkable similarity of Negroes in Nassau to Negroes in these other areas. Racial origin (West Africa) is assumed to be similar. The most notable difference affecting these populations is that while Bahamian Negroes have a high salt content in their water supply, and presumably also in food intake, the Negroes in St. Kitts have a relatively low salt intake in both food and water.[8]

Nassau water is gathered from numerous wells which vary in salinity. To obtain an impression of average salinity, a total of 76 samples were taken during

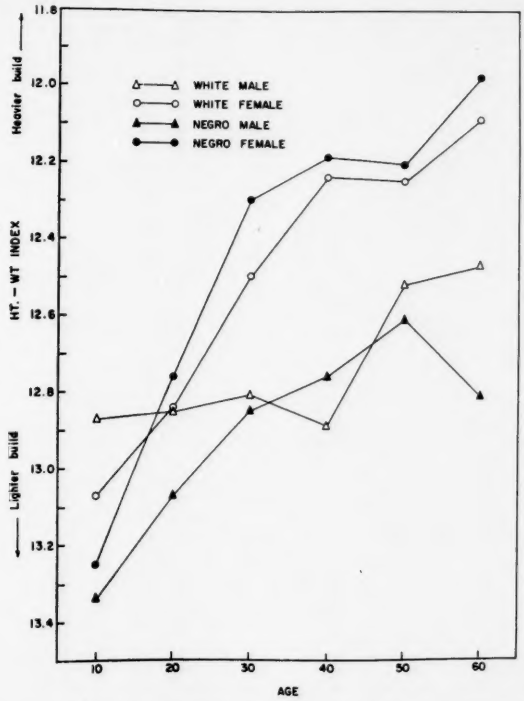

Fig. 5.—The mean of height-weight index by age, Negro and white races—Nassau, 1958.

the study period. Water was sampled in every area from which blood pressure measurements were taken. Essentially the same water was used by both races. Average salinity was 117 mg. per liter and ranged from 54 to 200 mg. per liter. Most eastern U. S. water supplies seem to contain less than 15 mg. per liter and occasionally as much as 50 mg. per liter. In some areas of the western U. S. salinity figures may be higher than those found in Nassau.[4]

Body Build.—In the present study data were obtained on height, weight, and arm girth. Height and weight were not studied separately, but rather by means of a ponderal index (height/cube root of weight). Such an estimate is not a direct indication of obesity, but represents leanness as opposed to heaviness. Negroes, on the average, appeared to be more heavily muscled than white persons. The present data show a tendency to an increase of pressure (both systolic and diastolic) with increasing heaviness. Although a low index usually represented

TABLE II. RELATIONSHIP OF HEIGHT-WEIGHT INDEX (HEIGHT/CUBE ROOT OF WEIGHT) TO BLOOD PRESSURE WITHIN AGE-SEX GROUPS—WHITE RACE, NASSAU, 1958

MALES				FEMALES (NONPREGNANT)			
HT.-WT. INDEX	SYSTOLIC MEAN	DIASTOLIC MEAN	NO. IN GROUP	HT.-WT. INDEX	SYSTOLIC MEAN	DIASTOLIC MEAN	NO. IN GROUP
			Age 6-9				
10	—	—	—	10	—	—	—
11	104.3	62.8	18	11	107.1	70.6	22
12	103.2	59.4	22	12	102.5	61.6	16
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—
			Age 10-19				
10	132.8	80.0	5	10	—	—	—
11	118.8	64.4	50	11	120.1	66.2	22
12	129.1	69.3	7	12	115.1	67.0	48
13	—	—	—	13	104.0	68.0	1
14	—	—	—	14	—	—	—
			Age 20-29				
10	140.0	79.3	6	10	134.1	83.2	12
11	123.4	73.7	47	11	118.5	72.8	69
12	114.7	65.3	3	12	108.0	76.0	1
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—
			Age 30-39				
10	—	—	—	10	123.2	81.4	13
11	128.3	80.2	41	11	119.1	74.7	45
12	117.4	70.5	24	12	114.7	80.7	3
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—
			Age 40-49				
10	—	—	—	10	151.1	92.6	19
11	132.6	81.9	27	11	140.6	84.5	24
12	133.5	82.8	17	12	157.0	78.0	2
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—
			Age 50-59				
10	126.1	82.2	7	10	157.6	91.2	15
11	141.3	84.3	19	11	146.8	86.3	28
12	—	—	—	12	—	—	—
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—
			Age 60+				
10	—	—	—	10	169.2	84.8	13
11	137.9	77.9	16	11	160.2	81.6	29
12	155.3	83.4	12	12	148.0	68.7	3
13	—	—	—	13	—	—	—
14	—	—	—	14	—	—	—

obesity, a heavily muscled person of the same height could have the same index as an obese person. The magnitude of the differences between means for different indices ranged from 1 to 78 mm. systolic pressure and from 1 to 54 mm. diastolic pressure, without discernible change in this regard with age, except in the young. Because of the size of the groups the study of Negroes yields more valid figures (Tables II and III). However, the pattern of progression of these mean indices by age (increasing heaviness) does not correspond to the pattern of mean blood pressure increase with age (Fig. 5). It appears that women of both races and men

TABLE III. RELATIONSHIP OF HEIGHT-WEIGHT INDEX (HEIGHT/CUBE ROOT OF WEIGHT) TO BLOOD PRESSURE WITHIN AGE-SEX GROUPS—NEGRO RACE, NASSAU, 1958

MALES				FEMALES (NONPREGNANT)			
HT.-WT. INDEX	SYSTOLIC MEAN	DIASTOLIC MEAN	NO. IN GROUP	HT.-WT. INDEX	SYSTOLIC MEAN	DIASTOLIC MEAN	NO. IN GROUP
			Age 6-9				
10	100.0	60.0	1	10	—	—	—
11	—	—	—	11	99.5	42.0	2
12	101.2	64.5	40	12	102.4	65.7	30
13	100.8	62.9	78	13	102.4	64.3	92
14	95.0	63.0	2	14	101.3	64.2	9
			Age 10-19				
10	—	—	—	10	188.0	120.0	1
11	135.5	73.0	2	11	126.2	68.4	9
12	119.6	72.8	57	12	117.0	69.0	92
13	114.4	67.7	202	13	110.0	67.9	153
14	108.5	67.8	29	14	110.2	65.9	27
			Age 20-29				
10	—	—	—	10	188.0	120.0	1
11	136.9	88.5	12	11	128.8	81.8	39
12	131.5	80.2	97	12	123.2	77.7	131
13	128.6	79.7	115	13	122.5	78.1	92
14	111.8	70.7	6	14	116.5	72.0	4
			Age 30-39				
10	—	—	—	10	138.6	89.4	13
11	146.1	98.7	11	11	139.3	90.3	43
12	140.6	88.8	54	12	134.8	86.5	75
13	133.5	85.9	47	13	132.5	80.9	36
14	184.0	110.0	2	14	111.3	68.7	3
			Age 40-49				
10	139.0	81.0	2	10	159.3	98.3	11
11	148.8	96.5	13	11	160.6	95.5	56
12	142.1	93.7	63	12	146.2	90.8	75
13	140.3	90.4	54	13	144.7	89.9	26
14	142.0	88.0	2	14	140.3	78.0	4
			Age 50-59				
10	—	—	—	10	172.5	95.5	13
11	181.3	100.7	6	11	171.1	96.5	20
12	150.7	92.5	31	12	156.1	91.7	37
13	144.6	87.3	26	13	158.4	91.1	16
14	—	—	—	14	—	—	—
			Age 60+				
10	174.0	84.0	1	10	196.8	95.0	4
11	170.9	98.3	7	11	186.1	94.6	17
12	186.1	90.5	8	12	171.0	88.5	22
13	151.6	84.0	17	13	172.5	85.3	18
14	210.0	110.0	2	14	153.0	90.0	2

of both races tend to be alike in this respect (increasing heaviness with age). Thus it seems that the body build and its correlate, arm girth (for which similar data were obtained), is a definite factor influencing blood pressure, but probably less important than was previously thought. Boe's[1] exhaustive work also suggests this conclusion.

Since women of reproductive age of both races showed relatively lower mean systolic pressures than males, an attempt was made to determine the effect of parity on blood pressure. Humerfelt and Wedervang[3] found that the average

blood pressure was inversely related to the number of children borne by the women they studied (the group was at the end of the reproductive cycle). Their finding could not be reproduced in this study, as seen in Table IV.

TABLE IV. RELATIONSHIP OF PARITY TO BLOOD PRESSURE WITHIN AGE GROUP—NEGRO FEMALES, NASSAU, 1958

PARITY	SYSTOLIC MEAN	DIASTOLIC MEAN	NO. IN GROUP
	Age 20-29		
0	127.7	81.7	38
1–2	122.9	78.0	89
3–4	125.8	81.5	66
5–6	120.1	79.8	19
7–8	123.8	77.6	5
9+	—	—	—
	Age 30-39		
0	129.5	81.9	59
1–2	139.1	86.9	37
3–4	130.9	85.4	42
5–6	141.0	89.6	27
7–8	135.7	86.4	14
9+	134.5	88.0	11
	Age 40-49		
0	163.5	96.0	21
1–2	148.5	91.6	51
3–4	151.4	91.3	36
5–6	149.7	91.6	27
7–8	150.0	93.6	16
9+	154.8	94.9	9
	Age 50-59		
0	165.8	90.0	8
1–2	151.4	92.0	14
3–4	165.9	96.9	17
5–6	161.9	95.5	15
7–8	167.8	90.8	5
9+	169.7	91.2	16
	Age 60+		
0	166.3	86.7	9
1–2	165.6	87.5	12
3–4	181.3	90.8	8
5–6	184.4	88.9	9
7–8	177.3	94.3	6
9+	179.3	94.5	8

SUMMARY

Results of a study of blood pressure levels in Negro and white residents of Nassau, Bahamas, have been presented. Persons for study were selected by means of probability sample design. The purpose of the study was to describe as accurately as possible the differing patterns of blood pressure with regard to race, age, and sex. The site was selected because of the opportunity to study the two races in a somewhat different environment and perhaps mode of life than previously reported by others. Also, the water supply of the area is known to be high in salt.

The following facts were disclosed:

1. A definite racial difference is seen. The pattern of progression of blood pressure with age is almost linear in the Negro. The white race, however, shows a flattening or "plateau" effect from the time adult ages are reached until middle

life, when mean blood pressure again tends to rise. This is seen in the means of both systolic and diastolic pressure, but most noticeably in regard to the systolic.

2. Sex differences are shown. Women of both races have lower mean systolic pressures during the reproductive years than men of their race. Negro men have slightly but consistently higher mean diastolic pressures than women almost throughout life.

3. Comparison with population studies elsewhere leads to the conclusion that Bahamian Negroes resemble Negroes elsewhere in the Western Hemisphere and Bahamian white persons resemble white people in other geographic locations in regard to blood pressure. A particularly provocative comparison is that of Bahamian Negroes with Negroes in St. Kitts (Leeward Islands),[8] since blood pressure patterns appear similar, despite high salt intake in the Bahamas and low salt intake in St. Kitts.

We are indebted to Dr. S. W. Hoobler, Dr. Marvin Moser, and Dr. H. J. Dodge for their extensive assistance with the planning of the study.

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APPENDIX

With the aid of the IBM 704 electronic computer, extensive statistical computations have been completed for each of the 14 basic measurements in the study. These 14 measurements are:

1. Systolic blood pressure, first reading.
2. Diastolic blood pressure; phase IV, first reading.
3. Diastolic blood pressure; phase V, first reading.
4. Pulse pressure (systolic minus diastolic phase V), first reading.
5. Pulse rate, first reading.

6-10. (Same as 1-5, but second reading.)

11. Height.
12. Weight.
13. Height-weight index. (Height/cube root of weight).
14. Arm girth.

Means, variances, and standard errors based on the probability sample design were computed for each of the 14 measurements by age, sex, and race subgroup.

To facilitate further mathematical studies of the structure of blood pressure distributions, descriptive means, variances, standard deviations, coefficients of skewness, and coefficients of kurtosis were computed for the 14 measurements by age, sex, and race.

Copies of these tabulations are available from the authors by request.

Psychiatry

CONSTRICTIVE PERICARDITIS: PSYCHOLOGIC ASPECTS OF CONVALESCENCE FOLLOWING PERICARDECTOMY

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Vol. 1
196

BETWEEN 1943 and 1951, 8 particularly instructive patients with constrictive pericarditis were treated surgically at The Johns Hopkins Hospital. These were young persons whose disease began during their teens. Following pericardectomy, only 4 were rehabilitated satisfactorily, despite the fact that all achieved relief from the constrictive pericarditis as determined by objective physiologic criteria. It was therefore decided to investigate these 8 patients from a psychosocial as well as cardiac viewpoint, in an effort to discern those factors which might be associated with their difficulty in symptomatic recovery. Though the group is too small for satisfactory statistical analysis, several factors have emerged which have an apparent bearing on the differences in rehabilitation among the various members of the group.

METHODS

This follow-up study was undertaken 4 to 14 years following the last pericardectomy. Each patient was subjected to a complete medical examination, a psychiatric interview, a biographical interview, and a brief battery of psychologic tests.

The psychologic tests used in this study were the Tennessee Department of Mental Health Self-Concept Test (to be referred to as the TDMH) and a brief form of the Minnesota Multiphasic Personality Inventory (MMPI) used to provide indices of depression and loss of morale.[2] Both tests are self-evaluative techniques which require the subject to indicate which of a number of statements

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pertaining to feelings, attitudes, and reaction tendencies are true or false in regard to himself and, in the case of the TDMH, to what degree true or false in general. The TDMH is so arranged and scored as to provide a profile of self-attitudes in the areas of physical functioning, moral-ethical values, emotional adaptability, primary or family group relationships, and secondary or social group relationships. A total self-concept score is also derived. The higher or more positive the scores on the TDMH, the more positive is the individual in his feelings about himself. Conversely, when the scores are low, or, in extreme cases, negative, the subject is revealing attitudes of instability, dissatisfaction, or inadequacy. The brief MMPI, as used in this study, provides three indices of depression and loss of self-esteem, two of them derived empirically in the original development of the test, and the third, a "morale-loss" index (M-L), derived empirically from a study using the briefer form of the test as also used here. The higher the scores on these indices, the greater the degree of depression, emotional disturbance, or morale-loss. The scoring in both tests is objective.

Each patient was informed of the purpose of the study and all were cooperative. It was apparent at the outset that rigid criteria to determine the extent of rehabilitation would be impractical since adequacy of rehabilitation must be conceived in terms of the social milieu in which each patient lives.

Medical examinations were conducted to determine the status of cardiac functioning in each patient. All of the patients had presented at operation three clinical findings characteristic of constrictive pericarditis, namely, elevated venous pressure, hepatomegaly, and dependent edema. At the follow-up examination all of the patients were noted to be free of these findings. (In none was there elevated venous pressure or hepatomegaly. In 2 patients [Cases 4 and 7] "minimal bilateral ankle edema" was noted but seemed to be related to the presence of varicose veins.) Therefore, all of these patients seemed to have achieved a satisfactory physiologic recovery following the operation.

CASE REPORTS

Case 1.—This 25-year-old white man was adopted into the family of a prison warden. His foster mother was a strict religious person who played a most important role in his childhood. As a boy he evidently rebelled against his mother's attitudes by getting into much mischief and by seeking among his classmates the acceptance he lacked at home. He was very active and personable, but fell behind in school because of recurrent illness. At 16 years of age he had successive bouts of pneumonia followed by the sudden onset of severe dyspnea and signs of constrictive pericarditis. The restrictions placed on his activities were almost unbearable to him. His customary means of "acting out" anxiety-produced tensions became limited by his illness, and frustration progressed to depression by the time he underwent pericardectomy, at the age of 19 years.

The results of the operation were dramatic. He was back in school after 2 months of convalescence, and he made up lost time so that he graduated with his class. He now works for a drug firm and is a voluble, confident salesman who sees "nothing but good days ahead." He is still prone to use physical activity to relieve tensions that arise in his life just as he had done prior to his illness. The relief he obtained by the cutting away of his pericardial scar could be likened to the snipping of a restraining leash that had kept him away from the physical activity so important to his psychic well-being.

Case 2.—A 29-year-old white man was the youngest in a family of 9 children. His parents died when he was quite young, and the rest of the family "rallied to each other's aid" in an atmosphere in which much value was placed on self-reliance and achievement. From the age of 3 he

had been afflicted with tuberculous osteomyelitis which eventually required the replacement of his right hip joint with a prosthesis and left him with a short leg. His childhood was marked by frequent moves from one brother to another, and by long periods of hospitalization. Two years before admission his pulse rate soared to 180, he became dyspneic, and constrictive pericarditis was diagnosed. He underwent pericardectomy when he was 14 years old. The results of the operation were excellent and he felt that he "was in a new world" when he left the hospital. At school he resumed his interest in gaining "business experience" that he felt he could use in future years. He worked after school and during the summer, and went to business school to try to acquaint himself with "business." His goal had always been self-reliance, and he had enough foresight to appreciate the steps necessary to attain this end. He married and began to raise a family after he became established as an accountant in a lumber firm, and apparently has good prospects of eventually owning the company. Striking goal-directedness has always been a prominent feature in his life. The pericardectomy served to release him from the limitations of his illness, and, indeed, enabled him to enter into a "new world" where he could compete in his chosen field.

Case 3.—This 25-year-old white man was the youngest of 3 boys in the family of a repairman in the Midwest. His mother was an active, domineering, nervous person in contrast to his father, who was quiet and submissive. The patient was an active, athletic type of schoolboy who showed qualities of leadership, and achieved maternal and self-approbation by effectively devoting his energies to school, athletics, and friends. At the age of 14 he was admitted to this hospital for pericardectomy after 2 years of severe symptoms. Though he had active tuberculosis, recovery was spectacular until, several months later, he developed tuberculous meningitis. Intensive treatment with dihydrostreptomycin left him completely deaf. After learning to read lips he went back to school, and eventually graduated with social and academic distinction from a small well-known college. At the time of this study he was looking for a job as a writer. His parents, who sensed that disappointment might lie ahead of him in this field, have tried to direct his energies to other areas. The patient resents this and has assumed the role of a coolly objective observer in the family. He feels that they do not appreciate his abilities and education. It is apprent that the onset of tuberculosis and constrictive pericarditis threatened him with a dependent position which he found quite unbearable. His residual deafness further challenged his possibility of achievement, but his desire for a career in writing enables him at least in fantasy to circumvent his limitations and maintain self-approbation and independence.

Case 4.—This 29-year-old white man was the only boy in a Pennsylvania Dutch farm family. His mother was a nervous, domineering woman who had chronic gall bladder disease and was frequently sick. His father was quiet, independent, and strict. They both spoke a local dialect and raised their children in a rather strict, ascetic religious community. The whole family was shy and nervous, and an older sister killed herself after a "nervous collapse." After 4 years of dyspnea and other symptoms characteristic of constrictive pericarditis, the patient underwent pericardectomy. He was 17 years of age at this time. His symptoms disappeared entirely, and when the doctors told him he was cured, he "never thought anything more about it." He lived at home doing farm work for 10 years until he decided to take a job as a truck driver in order to earn more money. At the time of the study he was planning to marry a girl who knew nothing of his intentions. He was opposed to having a family because "children are too nerve racking." He functions well in his own community environment, but his awkwardness, shyness, and autistic thought are quite obvious in other surroundings. His introversion and personality deficit are not particularly noticeable as long as he maintains a niche in his strictly local community. His pericarditis made him dependent on his family and held him back from doing work on the farm, so that pericardectomy served to return him to his niche of independent, quiet existence. His schizoid personality is least noticeable in this community where quiet, hard-working people live together and are able to avoid the tensions associated with frequent social contact.

Case 5.—This 28-year-old white woman was the older of 2 girls in a strife-torn family. Her mean, tyrannical father was a drunkard who often beat her mother in front of the children. After the parents separated the patient lived with her father, who raped her when she was 12 years of age. She then moved in with her mother, who was overprotective and oversympathetic. At this time she began to develop ascites and leg edema so that her peers ridiculed her, and she stayed home

from school to be with her mother. At the age of 14 she underwent pericardectomy. A partial decortication was done. The results were not impressive, and she was again operated upon 4 years later. She left the hospital asymptomatic and remained so for 2 years. It was during this period she met her husband. Early in her marriage her fears of sexual contact became apparent, and she developed many generalized complaints unrelated to constrictive pericarditis. However, a third pericardectomy was necessary at the age of 22, the results being excellent from a physiologic standpoint. Since then, the patient "doesn't remember anything" and feels as if she "isn't alive." She hides in closets and has contemplated suicide. She became pregnant, and the birth of her daughter has only served to make her problems more obvious. It was evident at the time of the study that she was severely depressed. There was abundant evidence to believe that she was emotionally disturbed before pericardectomy. The overprotection of her mother before and after operations, the lack of security and goals in life, and the primitive fears associated with sexual phenomena have all contributed to her poor rehabilitation.

Case 6.—This 33-year-old white man was an unwanted child who was given to an aunt as an infant. The aunt, whom he considered his mother, was an alcoholic who traveled with a circus. In her attitude toward the boy she fluctuated from great affection to extreme cruelty. When she was jailed for bootlegging, the court put the patient in a mental hospital because of nervousness, malnutrition, and inability to stay in school. After 3 years the boy returned to his aunt who continued her alternating love-hate pattern as he grew up. Symptoms of constrictive pericarditis appeared at the age of 17 and he underwent pericardectomy at the age of 22. Partial decortication gave little relief, so reoperation was accomplished 5 months later. Symptoms were relieved for 3 years but they returned and another pericardectomy was done. This relieved all the symptoms related to the disease, but failed to cure a draining osteomyelitic sinus over the sternum. Two years after this, when the patient was 28 years of age, his "mother" told him she was really his aunt, causing the boy to become severely upset. He was committed to a state mental hospital with the diagnosis of schizophrenia. He returned to his aunt after 5 months and lived with her until she died. At that time he was found in his "dead mother's" clothes, walking the streets. He was again put in a mental hospital where he was seen for this study. It was evident that extreme psychologic trauma and deprivation had contributed to his being a "psychiatric cripple" at an early age. The pericardectomies played little part in the production of his psychosis other than to get him reassurance of his aunt's love while he was hospitalized. He has no evident physiologic handicap at this time.

Case 7.—This 25-year-old white woman was the second child of 5 born to a rural laborer and his wife. Her mother was a nervous, anxious, overprotective person who dominated the quiet, submissive father. The patient was sick every winter as a child, and she made few friends, preferring to stay at home to help her mother with the household chores. At the age of 16 she developed symptoms of constrictive pericarditis and underwent pericardectomy at another clinic. Complete decortication was not accomplished and she did poorly postoperatively. One year later she had a complete decortication at this hospital and slowly convalesced at home. Although there were cardiac symptoms at times, no objective abnormality of cardiac function was found after operation. She remained at home so persistently that a letter was received from her father asking that she be given a "clean bill of health" so she could go to work. The time of this study was 6 years after the operation and she was still staying at home refusing to get a job because of her "heart condition." She has had no association with men or boys and she plans to live at home for the rest of her life, helping her mother. She has always been treated as a sick child by her overprotective mother and has tried to maintain this protective buffer between herself and society. Her basic insecurity relating to her interpersonal relationships has made her rely on her sickness as a means of satisfying her needs for affection and appreciation. The pericardectomy operations served only to confirm her impression of herself as an invalid and to reinforce the need for a buffer between herself and the rest of the world.

Case 8.—This 25-year-old Negro man was the second son of a merchant seaman. His childhood was spent largely with his mother, who was kind and industrious. The father and mother both died before the boy was 13, and he lived with a cantankerous, miserly aunt for several years. At 5 years of age, he contracted poliomyelitis and suffered a right foot drop and paralysis which

limited his physical activities to some extent. He attended school through the ninth grade, doing poorly, and showing complete disregard for persons of authority. After this he held several jobs which terminated because he did not show up at work or because of stealing from his employers.

At the age of 16 he developed edema and shortness of breath which progressed until, at 21 years of age, he was admitted to the hospital with constrictive pericarditis. Pericardectomy was accomplished and the patient was sent home free of symptoms. At home with his aunt he readjusted slowly. He was followed medically for 5 years and encouraged to get a job by the hospital physicians, but he felt he could not because of his "heart condition." At the time of the study he was a jobless, defensive, near-alcoholic derelict who had no direction in life as far as social or economic goals are concerned. He was living on state welfare funds and had no desire to get a job. His passivity, defensiveness, lying, and long history of disregard for authority figures, combined with complete lack of insight into his own problems, represent a serious personality disorder in a passive-aggressive type of person. His pericarditis and its treatment served to convince him that he was sick and allowed him to rationalize his avoidance of work and responsibility.

RESULTS OF PSYCHOLOGIC TESTING

The various scores obtained by the TDMH Self-Concept Scale and the brief MMPI are presented in Table I. It may be readily seen that there are fairly consistent differences between the patients who had made a good rehabilitation (Cases 1 through 4) and those who had not (Cases 5 through 8). The MMPI scores which provide measures of depression (*D*), obsessional ruminations and feelings of inadequacy (*Pt*), and loss of self-esteem or morale (*M-L*) most clearly indicate the difficulties in adjustment of the poorly rehabilitated patients in contrast to the rest. The profiles of TDMH scores, while showing slight overlap between the two groups of patients, are generally consistent with the rehabilitation status of the patients. Patient 3, whose TDMH scores were the lowest of the satisfactory group, is noted in the history to suffer deafness which may be presumed to interfere with his interpersonal relationships. However, as indicated by the various MMPI indices, his morale did not appear to be significantly decreased. Patient 8, who scored considerably higher than the other poorly rehabili-

TABLE I. SUMMARY OF PSYCHOLOGIC TEST SCORES OF PERICARDECTOMY PATIENTS

	PATIENT NUMBER							
	1	2	3	4	5	6	7	8
*TDMH Results**								
Physical self	28	21	17	30	−8	9	1	16
Moral-ethical self	23	26	21	31	−10	10	23	20
Emotional-adaptive self	13	18	11	32	−22	11	−1	25
Primary-group relations	25	24	10	31	6	12	21	21
Secondary-group relations	27	15	3	26	3	6	5	29
Total self-concept	116	104	62	150	−31	48	49	111
Brief MMPI Scale Results†								
Scale *D* (T-scores)	48	53	58	58	90	72	78	58
Scale *Pt* (T-scores)	48	48	54	58	96	62	69	60
M-L index (raw scores)	4	2	2	3	26	13	7	6

*The higher the score, the more positive is thought to be the subject's feelings about himself.

†The higher the scores, the greater is judged to be the degree of depression, emotional disturbance, or loss of morale.

tated patients on the TDMH, showed a trend to consider himself relatively physically incapacitated but otherwise adequate. This impression of his attitudes is also consistent with those revealed in his case history description.

DISCUSSION

In terms of objective physiologic criteria, the 4 patients (Nos. 1 to 4) who had been rehabilitated satisfactorily did not differ significantly from those (Nos. 5 to 8) who had not. These two groups did seem to differ from each other, however, in certain respects which we believe had an important bearing on the level of function ultimately attained after the operation.

The individuals in the first group (particularly Patients 1, 2, and 3) were notably active, goal-seeking persons. The advent of a chronic illness served seriously to disrupt a pattern of adjustment in which physical and social activity constituted an essential component. This interference was often accompanied by evidence of severe anxiety and/or depression, which is reminiscent of the reactions of some patients to the limitations on physical activity produced by disseminated lupus erythematosus as reported by McClary, Meyer, and Weitzman[3]. Pericardectomy seemed to free the individuals in this group to resume their pre-illness patterns of adaptation to life.

The patients in the second group impressed us as being quite different in their pre-illness mode of adjustment. Three of them came from backgrounds of gross trauma and depression. In general, all 4 individuals in this group had shown a much more passive, dependent pattern of adjustment prior to their illness, and pre-illness neurotic symptoms were common. In contrast to the first group, the occurrence of constrictive pericarditis and its surgical treatment did not disrupt a settled pattern of active adaptation to life, but rather served to reinforce and rationalize their insecurity and inadequacy. Their emotional difficulties continued after operation had corrected the constrictive pericarditis but then tended to be interpreted by the patient in terms of his past cardiac disease. This resultant obscuring of the end point of the organic disease has also been observed in delayed convalescence following other disorders.[4,5]

The condition of the patients, as revealed by the psychologic tests, could be interpreted, in the absence of other information, as the consequence of the disease. The history of pre-illness adjustments, however, suggests that the disease merely provided a refuge for previously established patterns of psychosocial disability.

SUMMARY

This study consisted of 8 cases of constrictive pericarditis seen at The Johns Hopkins Hospital between 1943 and 1951. All patients became ill during youth and were treated surgically with extensive decortication of the heart. They were re-evaluated in terms of cardiac function, level of rehabilitation, and personality functioning. Physiologic cure of the cardiovascular disease was attained in all 8. An adequate level of rehabilitation was reached by only 4. The quality of over-all rehabilitation following operation seems to be related to the personality development as reflected in pre-illness pattern of adjustment.

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Vol.
196

REACTIONS OBSERVED IN BOYS OF VARIOUS AGES (TEN TO FOURTEEN) TO A CRIPPLING, PROGRESSIVE, AND FATAL ILLNESS (MUSCULAR DYSTROPHY)

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ol. 13
1961

THE purpose of this article is to report on a study of the psychologic effects of muscular dystrophy, carried out in the setting of a day care program at the Payne Whitney Psychiatric Clinic over a 3 year period. The form of muscular dystrophy which strikes children has three significant characteristics. It is crippling, progressive, and fatal. It is important to note that these aspects of the illness are generally well known to its young victims. The children are at the same time aware of research activities. They and their parents can probably place some realistic hope in the finding of a cure on the one hand and the often relatively slow moving course on the other.

Research on the physiologic aspects of dystrophy has been carried out in the Payne Whitney Psychiatric Clinic under the guidance of Dr. Ade T. Milhorat over a 10 year period, during which interest in the psychologic aspects gradually increased. Special impetus was given to such interest by observations that the disability sometimes exceeded that which might be expected from the actual muscular impairment. In one such case, psychotherapy achieved dramatic results from the standpoint of increase in motility. In a report on this and other cases, Schoelly and Fraser[1] indicated that there were no distinct psychopathologic entities exclusive to dystrophic children and that severe emotional illnesses were no more common than in the normal population. They did, however, find a high frequency of minor to moderate psychopathologic disturbances, often of a neurotic character. Other studies of emotional adjustment in dystrophic children revealed a wide discrepancy of viewpoint, ranging from observations that they are extraordinarily well adjusted emotionally to those indicating marked immaturity and severe psychopathologic conditions.[2-4] Recent studies on the intellectual capacity and functioning of dystrophic children have tended to dispel a previous notion that an intellectual deterioration ensued as the illness progressed.[5] Findings in general have indicated a normal or dull-normal intelligence level.[3,4,6] As to their intellectual functioning, these children were noted most often to fall behind their contemporaries in grade level and to show special disabilities in reading and

Based on a paper presented at the annual meeting of the American Psychiatric Association, Philadelphia, Pa., 1959.

mathematical areas.[4] This was in essence the level of knowledge concerning these children at the time when a day care program was begun at this clinic in 1955. The purpose of the program was to examine psychologic reactions to the disease and to observe effects of the program on such reactions and over-all adjustment.

METHOD OF APPROACH

Fifteen children were studied, ranging in age from 10 to 14 years. The program was restricted to boys, since the disease occurs primarily in males. The children were observed over a period of 1 to 3 years. Six were studied for 3 years, 6 for 2 years, and 3 over a 1 year period. The children were confined to wheelchairs and were transported to the day care school each day. A public school teacher and an occupational therapist were engaged for the program. In almost every case, the children at the time of admission were behind their anticipated grade level and most frequently were assigned to different grade levels in different subjects. The educational approach was a conservative one, and the demands of the teacher were, in general, equivalent to those which might be made upon a group of normal children. On the other hand, the occupational therapist was instructed to be as imaginative as possible in stimulating the children in arts and crafts and recreational activities, which would be planned in terms of their limited motility. Within this setting psychiatric, psychologic, and social service studies were carried out. The nature of these will be described briefly.

Psychiatric Studies.—All children admitted to the day care program were initially given a thorough psychiatric evaluation. In addition, observations of the children within the group setting were made by psychiatrists. In several individual cases, play therapy was administered. Children were selected for this either for experimental reasons or for reasons of therapeutic necessity. In addition, all children taken into the day care program from the psychiatric inpatient department (for physiologic study) were thoroughly evaluated psychiatrically and received psychotherapy. In this manner, an experience was gathered with respect to children who showed psychiatric disturbances unusual for the group, as well as those with minimal or moderate disturbance.

Psychologic Studies.—These may be divided into two areas: (1) study of intellectual capacity and functioning and (2) study of personality factors and reactions by means of projective techniques. In the case of the former, psychometric evaluations included administration of the Wechsler Intelligence Scale for Children and in some of the earlier cases the Progressive Matrices and Stanford-Binet examinations. In addition, the children's progress in learning was evaluated by means of the Metropolitan Achievement Tests as well as the teacher's observations. With respect to the projective techniques administered, these included the Rorschach, the Thematic Apperception Test, and a series of drawings including that of the human figure. Certain experimental materials were also used. but these will not be considered here.

Social Service Studies.—Social service studies were carried out in an effort to obtain a picture of the adjustment of the child in the home setting and also any changes which might take place during the period of the project. Special attention was given to parental attitudes and approaches to the child and his illness. Family

interactions were explored. Much of this material has been separately reported by Henley and Albam.[7]

FINDINGS

None of the findings should be considered as necessarily representative of the population at large suffering from muscular dystrophy. The findings represent group trends within the population studied, and the number of subjects is admittedly small. It would be neither practical nor feasible to reproduce the data obtained by the projective techniques. The present article is more an overview of the project, while certain specific aspects of the materials will be presented in separate articles. The general direction of the data will be summarized and certain typical examples reproduced. A detailed analysis of the thematic materials will be reported elsewhere.[8] With few exceptions, percentages and other statistics on the Rorschach materials would be grossly misleading because of the small number of cases represented. The quality and focus within the subject's fantasies, both in story themes and Rorschach images, for the group as a whole formed the basis for the impressions reported and discussed herein. It should be indicated that the group studied was considered to be typical of individuals with muscular dystrophy.

Psychiatric observations tended to confirm previous findings that psychopathologic pictures in the children were generally mild to moderate in severity and that there were no psychopathologic entities characteristic of dystrophic children.[1] There were, however, various patterns of behavior and modes of defense which the children seemed to have in common. All of the findings, regardless of the source, suggested that the illness and its specific threatening features represented an ever present stress. This was evidenced, for example, by an apparent, very marked concern about the body shown in their figure drawings, by preoccupation in their recorded thematic fantasies with destructive forces over which they had little or no control, and by a tendency to dwell in fantasy upon catastrophic events. Clinically, however, they showed relatively little overt anxiety or depression as such in relation to the illness. Rather, their responses to the nature of the illness appeared to be characterized by rapidly shifting extremes between denial and acceptance. It should be understood that such qualities were inferred from indirect sources such as the nature of their fantasy in play therapy as well as in the recorded materials from picture stimuli. Denial is used here to mean denial of the consequences of their fate in relation to the illness, and acceptance refers to a conscious acceptance of the possibilities in store for them in terms of their physical prospects. Clinically, such side by side expressions of extremes in attitude toward the illness were often confusing to the therapist when he endeavored to deal with any deep anxieties presumed to accompany the shifts in the attitudes of the children toward their tragic condition.

Shifting attitudes and fluid movement from one pole to its opposite tended to characterize the children in general. For example (especially during the earlier periods of the study), in the school setting they tended to respond to situations with extremes of passive nonparticipation or suddenly impulsive aggressiveness. In the projective materials, this was reflected in particular when color served as

a stimulus challenge on the Rorschach cards. Their images in association with the emotional stirrings elicited by color were either highly aggressive or quite passive ones. The only exceptions to this pattern appeared in the few cases when the patients did not make use of the color stimuli at all. In their recorded fantasies, they often pitted crude strength against fragile weakness, marked aggressivity against inordinate submissiveness. Anxieties came to the fore when the children were faced with the challenge of relating to a group or even to another individual. Psychiatric observation included consistent reports of fluctuations between aggressivity and passivity and of poorly disciplined emotional controls over behavior. Indeed, these observations suggested that reactions to the group and to individuals alike seemed to unsettle these children far more than did the progress of their physical disabilities. An associated psychiatric finding was that the children seemed quite limited in their understanding of, and attendance to, the needs and feelings of others.

The projective studies displayed an inordinate reliance on fantasy life for basic satisfaction. For example, the following story produced by one of the subjects (in response to Card Fourteen of the Thematic Apperception Test) illustrates many features of the trend of the group as a whole. This card shows the silhouette of a man (or woman) against a bright window. The rest of the picture is totally black.

"This is a man and he's thinking of jumping out the window. He was in love with this girl and the girl left him. He wanted to kill himself. Just when he was going to jump out the window, she came back. Then one day she saw him with some other girl and she wanted to jump out the window. Just when he was walking in, she jumped. Then he jumped out. But he didn't die. He just got hurt and they took him to the hospital. Then he had these dreams in which the girl came to life. Each time he dreamt he used to call her name in his sleep. So he went to her funeral and stayed there. Everybody left. And she came out of the grave. He went to grab her and she just disappeared. Then she came back. Then he was chasing her. And he fell off the cliff. And he died. And they buried him right next to her. Then every night after that they came alive after twelve. This boy saw them both come alive. He ran home and told his father and mother. Nobody believed him. Then the next day he saw them again. Then his father and mother came with him and saw them going back into the grave. And his mother fainted. Then they called the police. They kept a watch on the grave and then one night at twelve they came alive again. And the police burned the grave and nothing was left, they just turned to bones."

This material shows the flavor of how the boys tend to rely on fantasy, the quality of vacillation between denial and acceptance of events, the aggressive features of their fantasy, the need to vary the obvious realistic development of the theme, the freedom and range of fantasy material, and the difficulty in accepting human limitations. Indeed, their fantasies often appeared to serve as an outlet for feelings in association with the restriction of motility which the disease imposed. Their fantasies were uncommonly free in the nature of motor activities imagined. An example of the extent of motor activities imagined and a representation of how these children *focus* their fantasy, Fig. 1 is a reproduction of a subject's response to the request to draw *a* person.

Note the focus on movement in many forms, the setting of playground activity, the vitality of the moving figures, and the detailed achievement of the drawing produced under muscle handicap of an advanced nature. In similar

fashion, the number of human figures in movement which appeared in their Rorschach images far exceeded the number of such images which would be expected from a matched nondystrophic group.

Although some of the adolescent boys (during the last months of the study) engaged in talk about sex or showed interest in this area, the youngsters seldom made direct sexual responses in the projective materials. In terms of the symbolic nature of their Rorschach responses, they often confused masculine qualities with the extreme of passivity and/or felt threatened by the aggressive potential of such images. In terms of sheer recurrence in numbers of responses, this finding went considerably beyond what might ordinarily be expected for their age grouping. Clinically, the onset of puberty seemed to constitute a stress for many of the children, who in the later stages of the study began to develop signs of overt anxiety apparently related to sexual matters. This, of course, was understandable

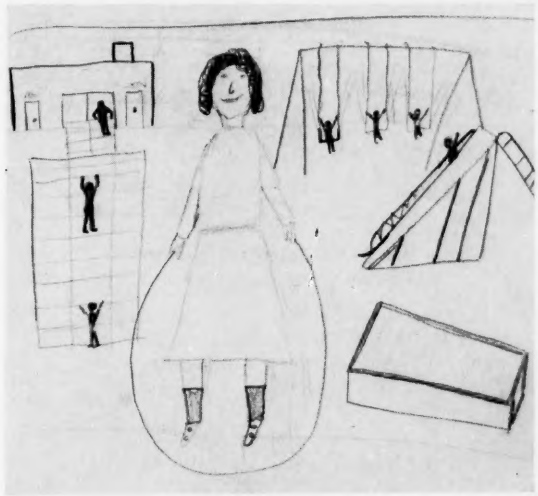

Fig. 1.

when their limitations are considered, but the youngsters were reluctant to discuss their concerns about sexual matters, and it was difficult to deal in any direct manner with them in psychotherapy.

Psychologic testing of intellectual capacity confirmed those recent findings which have indicated that the children suffering from this illness possess an essentially normal intelligence, at least in the verbal sphere, and that, so far as is known, it is not affected by the progress of the disease. It should be kept in mind that the scores shown in Table I refer only to verbal intelligence. The standard intelligence tests which include items related to motor skill tend in most cases to discriminate against these children in terms of scores obtained, since their physical handicaps limit their motor facility. If the intelligence quotients include performance items, in which success depends upon an intact motor function, then the I.Q. scores would be lower, often falling within the dull-normal or borderline ranges. For purposes of predicting school progress in association with intellectual

TABLE I. MEANS, STANDARD DEVIATIONS, AND RANGES OF AGE AND VERBAL INTELLIGENCE FOR THE SUBJECTS

NUMBER OF SUBJECTS	VERBAL I.Q.			AGE (IN YEARS)		
	MEAN	S.D.	RANGE	MEAN	S.D.	RANGE
15	103	11.7	90–130	12.0	1.75	10–14

capacity, it was felt that the intelligence of a youngster with muscular dystrophy was best measured by means of the verbal tests of the Wechsler Intelligence Scale for Children and, perhaps, the Progressive Matrices Test.

Although Wechsler performance (motor) items are not included in the figures of Table I, a comparison of the performance scores with the verbal scores obtained by these children revealed certain unusual features. At least in some cases, there was not nearly so wide a discrepancy between performance and verbal I.Q.'s as might have been expected. Four of the 15 subjects achieved a performance I.Q. slightly higher than their verbal levels. As far as psychological theory is concerned, and especially in regard to developmental psychology, this may have been one of the most interesting findings of the study. There was very little evidence that the children, including the brightest and most gifted ones, tended to compensate for motor deficit by concentration on verbal activities and interests. All of the dystrophic children demonstrated strong motivations toward accomplishing motor tasks to the best of their abilities. As a group they were not readers and, in fact, were poorly informed about the world around them.

Within the day care program, there were some changes in the patterns described. The children in general managed in time to form a more cohesive group and to exercise some measure of control, particularly over aggressive behavior. Parents reported that the children displayed in the home a more independent attitude and were generally more self-reliant. During the period of the program, in spite of increasing muscular impairment, the children were able to continue most of their activities in occupational and recreational therapy without noticeable change to the casual observer. In schoolwork, the teacher reported that lack of motivation sometimes represented a problem. Nevertheless, in some instances, the children were able to catch up in their work and reached a grade level more or less equivalent to their ages. In many instances they were able to accomplish a year's work in a year's time in this special setting.

DISCUSSION

To summarize the findings of greatest interest in these patients, we would indicate the following: relative absence of serious emotional illness, relative absence of overt anxiety or depression, absence of predominant modes of behavior and attitudes in favor of "seesaw" responses, relatively retarded development of conscious controls over behavior especially in the area of interpersonal and group activities, excessive reliance on fantasy life as a source of satisfaction and as an

outlet for tensions, along with the free and markedly fluid nature of these fantasies including motor and aggressive activities. In the area of intellectual functioning, the most striking feature appeared to be the high degree of motivation for motor activities, with, in some cases, remarkable accomplishments in these areas.

Before endeavoring to discuss these findings, it should be said that they are not necessarily characteristic of chronic disease, or fatal disease, or crippling disease. For example, studies of disabled nondystrophic children have suggested a focusing upon verbal activities,[9] as well as limited drive with respect to motor activities.[10,11] In a variety of disabling, chronic, or fatal diseases in adults, denial as a mechanism has been noted.[12-14] Although the extent of denial varied in these patients, there was no emphasis on the contrast between denial and acceptance noted in the dystrophic child. In studies of children with a fatal disease such as leukemia, it has been suggested that a frequently observed resigned, fatalistic, or even depressed attitude may serve as a mechanism against arousal of intense anxiety.[15,16] In general, therefore, it would appear that the findings reported in dystrophic children are relatively unique. Perhaps they can be explained in part on the basis of the nature of the disease itself, combining as it does disabling, chronic, and progressive features as well as a fatal outcome, all of which components are generally known to the children.[17]

Before discussing some of these unique patterns common to the disease, a word should be said about the apparent absence of any specific type of emotional illness or disorder characteristic of dystrophic children. The probable explanation for this lies in individual variations in personality dynamics and environment of the individual children.

In considering common patterns and modes of defenses, however, the nature of the illness and the mode of life and activity which it generally imposes upon the child and his family assume primary importance. Of special significance are the restriction upon motility and the threat of progressive disability and death, which are always present. In addition, overprotection so often reported in mothers of these children[7] is important and may lead to relative isolation and dependence of the child. He cannot, in any event, lead a normal life with his peers, he must sooner or later retire from a normal school setting, and his social activities may become reduced to a minimum, except for those especially sponsored by associations for disabled children. This relative isolation as well as the progressive muscular weakness itself may retard development of conscious controls over behavior so frequently observed in these children. Indeed, it may also explain the reliance on fantasy life for gratification of needs and the frequent unchecked content in their fantasy of assertive or even violent action. For example, within the day care program one youngster revealed a recurring fantasy of bringing a knife to school and killing a youngster at whom he was angry. As far as the practical aspects of the situation were concerned, these revelations produced little anxiety among the staff, who knew that even if the child did bring a knife, he would never have the strength to carry out such an action. It seemed too that the patient had a certain awareness of this fact. As such, the fantasy seemed far less threatening to him and far less in need of control than it would be in a normal youngster. In another sense, the illness may promote the failure of development

of predominant conscious attitudes by giving rise to the denial-acceptance pattern which the children demonstrate. Such a defense pattern seems relatively successful in warding off anxiety with relation to the illness, and it is in fact difficult to imagine what other mode of defense would be available to a young child stricken with a progressive and fatal disease of long duration. However, it appears necessary for him to maintain this kind of general pattern in dealing with stress at the expense of a more mature development of conscious controls and attitudes in his interpersonal activities.

The fact that these children appear to be relatively free of overt anxiety with respect to their illness, in contrast to their impulsive and unpredictable behavior in groups, may explain in part the variations in opinion as to the overall adjustment of these children. It is possible that those authors who have considered the children free of psychopathologic disturbance have focused upon the manner with which they react to their illness, which seems superficially to represent a good adjustment. The individuals who have regarded these children as immature and markedly disturbed have probably observed them most frequently in the setting of group activities.

Of special interest, in view of the essentially immature patterns of defense and excessive reliance on fantasy for gratification, is the relative absence of serious emotional illness in the group. There are two possible factors which may serve to explain this. One is the relative protection from the stresses of life which these children receive at the hands of their parents. The other, and perhaps more important factor, is the constant threat to survival which the illness itself represents. This continuing, real stress, although it could give rise to anxiety and contribute to retardation of emotional development, may also serve as a check upon more serious development of a psychopathologic condition, as other external stresses sometimes do. Thus, the situation may be analagous to observations made so often in adults under apparent severe external stress (such as in wartime) who fail to develop serious psychopathologic states until after the stress situation has abated. Or, it may be analogous to the situation of emotionally ill individuals who demonstrate a favorable response in terms of their illness when an external crisis occurs. Thus, the threatening progressive and fatal nature of the illness may create a situation in which the child devotes a considerable amount of his energy to devices to ward off anxieties concerning it, so that he may become retarded in other areas. But at the same time, it may serve as a protective device against a more serious emotional illness to which the nature of his defenses might otherwise make him vulnerable.

It seems particularly important to note that the motor drive is apparently so psychologically important to the dystrophic child that a progressive disability does not diminish his interest in and motivation toward motor expression. This suggests that we need to know more about the theoretical nature of compensation. In other forms of crippling illnesses, it is interesting to note that reported studies[9-11] have suggested a different pattern of reaction to motor handicaps. However, the unique quality of a progressive motor loss should be kept in mind, since it doubtless creates something different from a relatively static loss existing either from birth or a later specific time. The dystrophic child experiences a gradual

loss from a previously higher level of skill, and his ebbing strength is quite apparent to him. This loss is somewhat analagous to a reversal of motor development. In this sense, the child's experiences within the developmental pattern have been much more like those of the normally developing child than would be true, for example, in cerebral palsy. The keen concern of these dystrophic children with motor expression may have relevance to the psychologic importance of motility in personality development in general. At least in the present group, this fascination with motor activities came into repeated focus in a way that could not be explained simply by the fact that the day care program may have stimulated them to some extent in this regard.

Finally, the advisability of attending to psychologic aspects of muscular dystrophy must be stressed. The gains of the children within the day care program would indicate that the use of therapeutic and educational techniques appropriate to them might tend to forestall the falling behind in intellectual and emotional growth generally observed in the children. The eventual discovery of a cure for this disease is a real possibility, so that to a certain extent the dystrophic patient must be prepared for the future like any other child. Even within the setting of the present bleak situation facing the children, attention to psychologic factors may make the difference between relative well-being and inactivity and unhappiness.

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SUMMARY AND CONCLUSIONS

A day care program for dystrophic boys, with the purpose of studying reactions to the disease, has been described and the findings reviewed. The latter have included relative absence of serious emotional illness, "seesaw" responses and poor controls, and high degree of motivation for motor activities. The following conclusions would seem to emerge:

1. The failure of the dystrophic child to develop dominant modes of conscious attitudes and adequate controls over behavior, in favor of seesawing and impulsive responses, may be understood in terms of reactions to the illness and its consequences.

2. Motility appears to be so important to these children psychologically as well as physically that progressive disability does not diminish interest in these areas.

3. Absence of serious psychiatric illness in these cases may be in part due to protection from stresses of normal life and in part concerned with reaction to the reality stress which the illness represents.

4. Experience in the day care program suggests that some of the difficulties may respond to specially designed teaching and therapeutic techniques. The importance of increased attention to psychologic aspects in these children is emphasized.

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ADVANCES IN CANCER CHEMOTHERAPY

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THOSE who manifest a major interest in the field of cancer chemotherapy must at times tread lightly to avoid the label of "cancer quackery." It should be stated clearly then, at the outset of this paper, that the cure of cancer has been effected only by surgical or radiation therapy. After many years of searching for better methods of treating cancer, however, and even with the major developments in more radical surgery and radiotherapy, our treatment of malignant disease is at best discouraging. It is of interest to record some observations from a textbook of medicine published over 100 years ago: "Cancer . . . is seldom effectually cured by an operation. In four cases out of five, the disease breaks out in another part of the body in the course of a year after a cancer has been thus removed. Cancers situated in the skin may be effectually removed either by the knife, by application of plasters, or by caustic, and sometimes the disease does not return even where the seat has been in a gland, for instance, in the breast."*

Hope for the cure of cancer by use of some systemic drug is as ancient as knowledge of cancer itself. Cancer chemotherapy probably had its origin about the middle of the nineteenth century when Lissauer[1] used Fowler's solution in the treatment of leukemia, but the modern approach to the drug treatment of tumors developed during World War II with the introduction of nitrogen mustard.[2] Since then hundreds of chemical agents have been introduced with varied degrees of enthusiasm, but only a few of these have proved to have clinical application. One could compare the present status of cancer chemotherapy to the "silver bullet" era of Ehrlich. With the discovery of the efficacy of arsenical preparations in treating one form of infectious disease, researchers began to develop chemicals which could poison other bacteria, eventually leading to the

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*Comfort, J. W.: The Practice of Medicine on Thomsonian Principles, Adapted as Well to the Use of Families as to That of the Practitioner, Philadelphia, 1843, A. Comfort, Publisher, Coates, Printer, p. 330.

age of antibiotics. Research workers in the field of cancer have been seeking means by which to poison cancer cells. The analogy is perhaps appropriate.

PATHOPHYSIOLOGIC CONCEPTS

In designing drugs to be effective specifically against cancer cells, it is most important to understand any fundamental biochemical differences between cancer cells and normal cells. Although it has been shown that cancer cells do not contain any chemical substances not found in normal cells, there is a quantitative difference in that cancer cells exhibit marked increase in aerobic and anaerobic glycolysis.[3] As research continues, other differences may be found. But even with our present knowledge, the fact that cancer cells are rapidly metabolizing cells has led to the development of certain antimetabolites which are taken up avidly by the tumor cells. Yet, with certain exceptions, antimetabolites have been disappointing in cancer chemotherapy. Attempts at altering the environment of the tumor cells have been somewhat more successful in certain tumors. Thus hormonal therapy appears to exert beneficial effects by changing the milieu of the cancer cells.

In the search for effective cancerocidal drugs, considerable emphasis must be placed upon the development of some agent which has a selective effect against neoplastic cells. While no such compound has yet been discovered, it seems plausible that specific poisons which will inhibit certain enzymes necessary for the metabolism of tumor cells may eventually be developed. Such a concept finds credence in the work of the famed cellular physiologist, Otto Warburg. Thirty years ago Warburg[4] advanced the theory that cancer originates when a normal cell becomes neoplastic following injury to its respiratory system. The cell then manages to survive by adopting anaerobic metabolism. More recently Warburg[5] has summarized his work in cellular respiration and reiterated his theory of the origin of cancer cells based on experiments carried out with ascites tumor cells. He theorized that following irreversible injury to the respiration of normal cells, a reversion to a more primitive form of respiration occurs and the cells derive their source of energy from fermentation rather than from oxidation. Such a change involves a long passage of time before the cells can convert into undifferentiated cells which we recognize as cancer cells. Further studies show that the respiration of malignant tissue is considerably less than that of normal tissue, while glycolysis is markedly increased. From these observations it might be inferred that there is a difference between the respiratory enzyme system of tumor cells and that of normal cells. It has been suggested that the basic derangement is an alteration in the hexokinase reaction of glucose phosphorylation.[6] (It is only fair to mention that Warburg's concepts have been questioned and criticized.[7,8])

CLINICAL ASPECTS

I. Classification and Clinical Application.—

Certain of the biochemical and physiologic theories just discussed have had practical application in the design of cancer chemotherapeutic agents. For the

TABLE I. "FUNCTIONAL" CLASSIFICATION OF ANTICANCER DRUGS

I. *Cytotoxic Drugs (Antimitotic).*—
- A. Alkylating agents
  - 1. Nitrogen mustards
  - 2. Ethyleneimines
  - 3. Sulfonic acid esters
- B. Antibiotics

II. *Cytostatic Drugs (Antimetabolic).*—
- A. Folic acid analogues
- B. Purine analogues
- C. Glutamine analogues
- D. Pyrimidine analogues

III. *Cytolytic Drugs (Hormonal).*—
- A. Androgens
- B. Estrogens
- C. Corticosteroids

sake of organization these chemicals have been grouped into three general categories: cytotoxic, cytostatic, and cytolytic drugs (Table I).

A. Cytotoxic Drugs (Antimitotic).—These are the tumoricidal agents which actually have the ability to destroy cells during growth. In a sense they can be likened to bacteriocidal drugs. As a matter of fact, some of these compounds are antibiotics. They may act by poisoning cell enzymes. Cytotoxic drugs are divided into two main classifications, alkylating agents and antibiotics.

1. Alkylating agents: These are compounds which have the ability to combine with various constituents of cells by attachment of an alkyl chemical group to an oxygen, nitrogen, or sulfur atom of proteins, nucleic acids, and other cell constituents. Whether the damage to the cell is the result of injury to the nucleic acids of the cell or indirectly through enzyme inhibition is not well known. There is a possibility that both actions are important.

a. Nitrogen mustard compounds: The first of the alkylating agents is nitrogen mustard and its analogues. Once it was learned that nitrogen mustard exhibited antitumor activity, many compounds were developed in an attempt to enhance the action of mustard by altering its specificity. With knowledge of the metabolic requirements of specific tumors, the mustard radical was attached to various amino acids, sugars, vitamins, and pyrimidine precursors, in the hope that the "carrier group" would increase the avidity with which the tumor cells might take up the drug. Attempts were also made to concentrate mustard in certain tissues of the body. Thus chloroquine and quinacrine mustards were synthesized in hopes that they might concentrate selectively in malignant tumors of specific organs, e.g., the nervous system and the liver.[9]

At the present time only a few of these variations have been found useful. In Europe mannitol-mustard is available commercially under the trade name of Degranol.[10] Investigation has been carried out in this country using phenylalanine-mustard in the treatment of malignant melanoma.[11] A mustard analogue,

Endoxan, used in Europe for the past few years, is now being introduced in the United States as Cytoxan. Perhaps the most important variation in mustard compounds has been the development of oral preparations. One of these, chlorambucil,[12] is now available in 2 mg. tablets under the trade name of Leukeran and is administered in 6 to 12 mg. doses (0.1 to 0.4 mg. per kilogram daily). More recently the mustard radical has been linked to a pyrimidine precursor to form uracil-mustard (U-8344).[13] Since it is known that tumors require a large amount of uracil to form nucleoprotein, it was hoped that this drug would be taken up by the rapidly proliferating cells with considerable avidity. Uracil mustard exhibits antitumor activity considerably greater than chlorambucil, milligram for milligram, and is administered in doses of 1 to 2 mg. daily (0.01 to 0.04 mg. per kilogram daily).[14]

For the most part the mustard compounds find their greatest clinical application in the treatment of the malignant lymphomas, chronic lymphocytic leukemia, and to a lesser extent, multiple myeloma. Both chlorambucil and uracil-mustard are beneficial in relieving the pain of multiple myeloma and perhaps reducing the plasmocytic infiltration of the marrow. Actual healing of the osseous lesions, however, has not been observed. These compounds are easier to administer and do not produce the severe toxic manifestations of urethane. Certain carcinomas may be improved with nitrogen mustard compounds; ovarian carcinoma may regress dramatically.[15] We have observed continued regression of ovarian carcinomas in patients taking uracil-mustard daily for over a year.

Once a course of oral mustard is embarked upon, we prefer to administer the drug for several months even though all clinical manifestations of the disease have regressed. If toxic manifestations develop, interruption of therapy for a few days will usually produce improvement and therapy may be reinstituted, usually at a somewhat lower dosage. In this way the drugs have been administered continuously for up to 2 years in a large number of patients, generally without serious or irreversible toxic effects and with continued clinical improvement.[14,16]

Because of the inconvenience of administration, the severe gastrointestinal upset associated with its administration, and the bone marrow depression which usually follows therapeutic doses, nitrogen mustard itself has somewhat less clinical use at the present time than formerly. It is most helpful in reducing large lymphoma tumor masses in the shortest period of time. In the treatment of solid tumors, nitrogen mustard has produced significant regression of ovarian carcinomas[15] and may be dramatic in relieving the superior vena caval syndrome due to bronchogenic carcinoma or other tumors. The effect, however, is usually transient.

b. Ethyleneimines: These are examples of monofunctional alkylating agents. Probably the first of these to show antitumor activity was triethylenemelamine or TEM.[17] This was followed by the phosphoramides, TEPA[18] and thio-TEPA.[19] These agents have had a somewhat limited place in cancer chemotherapy but have led to the development of other related compounds. Attempts have been made to utilize the active ethyleneimine radical and increase its efficacy by combining it with chemical carriers. Domagk[20] combined the ethyleneimine radical with a quinone and hydroquinone molecule to form a new series of compounds.

The first of these compounds is known as E-39 and has the disadvantage of being soluble only in alcohol. Therefore, when administered intravenously, it causes severe irritation of the veins. The hydroxyl variant of this, A-139, is water soluble and is considerably less irritating. We[21] have utilized these compounds in the treatment of over 120 patients with various neoplasms. While their general efficacy is limited, impressive though temporary regression of tumor masses has been observed in a number of difficult neoplasms.

More recently the ethyleneimine radical has been combined with the antimetabolite, urethane, to form the so-called "dual antagonists."[22] Such compounds have the theoretical advantage of acting simultaneously against cells by diverse mechanisms without the differential rate of absorption which would occur if the drugs were administered individually. In addition, since cells may exhibit different degrees of selectivity for various chemicals, the more readily assimilated chemical compound would increase the localization within the cell of the less readily selective grouping. The administration of this ethyleneimine-carbamate, known as AB-100, is via the intravenous route and in the limited clinical trial thus far irritation of the veins has not been noted. Antitumor activity has been observed in a few of the patients treated.

c. Sulfonic acid esters: Another group of alkylating agents are the sulfonic acid esters. Myleran[23] is certainly the best known and most widely used of these compounds. It appears to be most useful and the drug of choice in chronic granulocytic leukemia. It is available in 2 mg. tablets and is administered in dosages of 4 to 10 mg. daily until a remission occurs. Once the remission has been achieved the drug may be discontinued but about half of the patients require a small maintenance dosage. A course of Myleran may be repeated as often as necessary in those patients who do not require constant maintenance.

d. Epoxides: Only preliminary work with this new group of alkylating agents has been done.[24] Activity against lymphomas and certain solid tumors has apparently been demonstrated.

The toxicity of all the alkylating agents is similar, but varies in intensity. The immediate toxic effect is manifested in the gastrointestinal tract, with nausea, vomiting, diarrhea, and abdominal cramping pain. Some degree of bone marrow depression occurs in most patients but serious depression can usually be prevented by cautious administration or discontinuation of therapy at the earliest signs of impaired hematopoiesis. With severe toxicity, some degree of alopecia may also be noted.

2. Antibiotics: As one might anticipate, various antibiotics have been used in an attempt to inhibit cell proliferation. While there has been initial enthusiasm for a variety of antibiotics, subsequent studies have not verified their initial promise. At the present time none of the antibiotics is recommended for use alone in the treatment of tumors. Actinomycin[25] has perhaps had the greatest clinical application, particularly for certain tumors in children.[26] It has also been used to "sensitize" tumors to radiotherapy and it appears to exert some synergistic effect in this regard.[26,27] Mitomycin[28] and Sarkomycin[29] have been reported to be helpful agents by investigators outside the United States but studies in this country have not yet confirmed their efficacy.[30] Rare reports of the efficacy of

Furacin in the treatment of testicular tumors have appeared.[31] Some investigations are now under way in this country evaluating a new antibiotic, streptovitacin.[32]

B. Cytostatic Drugs (Antimetabolic).—The design of compounds which would have a specific competitive or substitutional action for certain cellular metabolites probably had its origin with the introduction of the antifolic acid compounds.[33] Since that time numerous compounds have been synthesized which are able to inhibit cellular enzymatic reactions necessary for the synthesis of nucleoproteins. As discussed earlier, intensive research has failed to reveal any enzyme present in the cancer cell that is not present in normal cells.[3] On the other hand, recent research shows that a number of enzymes present in normal cells are absent from cancer cells.[34] Peculiarly, these missing enzymes have a catabolic action, particularly in the degradation of purines, pyrimidines, and amino acids. Thus normal cells should be able to destroy the antimetabolites, while tumor cells lacking the catabolic enzymes would not be able to do so.[35] With this in mind, it may be possible to synthesize antimetabolites with a selectivity of action, depending on the enzymatic defect of the cell. This should be a fruitful field for future research.

It is paradoxical that in spite of the tremendous interest in antimetabolic therapy in recent years, these agents have not been very effective against solid tumors. On the other hand they are our major chemotherapeutic agents in the treatment of acute leukemia. Because use of the antimetabolic agents requires considerable experience and special knowledge, the various agents that have become available for clinical application will be discussed only briefly.

1. Folic Acid Antagonists: Although a number of antifolic acid compounds have been synthesized, amethopterin and Aminopterin have had the most extensive clinical use. Folic acid antagonists have their greatest application in the treatment of acute lymphocytic leukemia. In our experience some patients with acute granulocytic leukemia have benefited if they had previously responded to other purine antagonists. Recently the work of Li and Hertz[36] has revealed that amethopterin is capable of producing regression of metastatic choriocarcinoma in women. Apparently the drug is not effective against this tumor in men. Amethopterin is available as Methotrexate in 2.5 mg. tablets. Parenteral preparations may also be used.

2. Purine Antagonists: A number of analogues of adenine and hypoxanthine are effective in inhibiting purine synthesis. Of these, 6-mercaptopurine and 6-chloropurine have had the widest clinical application. These compounds are most effective against acute leukemia, especially acute lymphocytic leukemia. Patients with acute granulocytic leukemia may occasionally respond. Chronic granulocytic leukemia may also be effectively treated with 6-MP but Myleran is probably easier to use. Once the terminal "blastic" phase of chronic granulocytic leukemia develops, 6-MP may be useful in inducing a remission. At this point none of the alkylating agents are of value. 6-MP is available in 50 mg. tablets under the trade name of Purinethol.

3. Glutamine Antagonists: While glutamine is necessary in at least three steps of nucleic acid synthesis,[37] the presently available glutamine antagonists

are of limited clinical value. Azaserine and DON (6-diazo-5-oxo-L-norleucine) have shown antitumor activity,[38] but neither compound appears to be very effective clinically. Azaserine has been used in conjunction with other antileukemic agents in an attempt to delay resistance.[39]

4. Pyrimidine Antagonists: Thus far most of the widely used antimetabolites have been those which exert inhibitory actions on nucleoprotein synthesis via the purine pathway. Until recent years no effective compounds were developed which would serve as antimetabolites in the pyrimidine pathway of nucleoprotein synthesis. Now a number of such drugs are available with somewhat limited clinical application. 6-Azauracil[40] and 5-fluorouracil[41] have been tried, but their toxic reactions severely curtail their widespread use. 5-Fluorodeoxyuridine (FUDR) appears to exert distinct action against certain tumors and is considerably less toxic than 5-fluorouracil.[42] FUDR has been able to induce remissions in acute leukemia after the patient has become resistant to all other forms of therapy, but apparently the remissions are short lived.[42]

Urethane has long been used in the treatment of chronic leukemia and myeloma. Recent evidence suggests that urethane acts as a pyrimidine antagonist.[43] A number of other agents are now available with less toxicity than urethane and with efficacy equal to or surpassing it.

5. Vitamin Antagonists: Compounds have been developed which serve as antimetabolites against pyridoxine,[44] riboflavin,[45] and nicotinamide,[46] and these agents have been shown to inhibit various forms of experimental neoplasms. They have not, however, been effective clinically.

C. Cytolytic Drugs (Hormonal).—It has been known for a long time that hormones may influence the growth of both normal cells and tumor cells. The mechanism by which this influence is exerted is not yet understood but it may well be related to factors which control the growth of tissue in general.

1. Androgens: While male hormones have been used in a variety of neoplastic disorders, their only specific indication is in the treatment of breast carcinoma. As a "rule of thumb," androgenic substances are the treatment of choice in patients with metastatic breast carcinoma who are premenopausal, menopausal, or within four years past the menopause.[47] Older patients may also be benefited, but estrogens are superior in this group.[47] Testosterone propionate may be administered intramuscularly 3 times a week, in doses of 50 to 100 mg. for a minimal total dose of 3 Gm. A new oral androgen, fluoxymesterone (Halotestin),[48] has simplified therapy somewhat, and allows for easier individual regulation of dosage, 30 to 50 mg. being the average daily dose. Improvement may be seen in a week or so but many patients require up to 3 months of androgenic therapy for objective evidence of benefit. Remissions with androgens usually last between 6 and 12 months although an occasional patient may do well for a longer period of time.[47] Once there is clinical evidence of relapse, either estrogens or steroids may be used and improvement may again be obtained. In our experience liver metastases have not been helped by androgens, or for that matter by estrogens. Although the usual masculinizing side effects may occur during androgen therapy, it is our feeling that these are somewhat less marked with the use of Halotestin. This, however, remains to be more clearly ascertained.

Vol. 13
1961

2. Estrogens: Female hormones may be beneficial in cancer of the breast of both male and female, and in prostatic carcinoma. In women beyond the fourth postmenopausal year, estrogens are the treatment of choice for metastatic breast carcinoma. Even younger women, beyond the age of 30, who have had either an induced or a natural menopause, may exhibit tumor regression with estrogens.[47] Remissions last somewhat longer than with androgens. Diethylstilbestrol is the agent most commonly used, administered daily in 15 mg. or a somewhat higher dosage.

The majority of patients with carcinoma of the prostate derive gratifying results from estrogenic therapy. While most patients respond to 5 mg. of diethylstilbestrol daily, a few require considerably larger quantities. Once improvement is noted, maintenance should be continued indefinitely with doses of 5 mg. or less.

3. Corticosteroids: Adrenocortical hormones are perhaps the most versatile drugs in the management of cancer. Since adrenal hormones are known to be potent lympholytic agents, it could be anticipated that they would be useful in the treatment of leukemias and lymphomas. Dramatic benefit, often resulting in complete hematologic remission, may be seen in acute lymphocytic leukemia. Patients with chronic lymphocytic leukemia or lymphosarcoma may have striking regression of tumor masses and splenomegaly under steroid therapy. There is, however, a paradoxical response noted in a number of these patients; a rise in the total circulating lymphocytes may be observed in spite of the regression of the tumor masses.[49] With continued therapy the lymphocyte count falls but usually does not reach the pretreatment levels. The hormones are particularly useful in complications of these disorders, namely, hemolytic anemia and thrombocytopenia. Even small doses of steroids may promptly correct anemia or stop the bleeding of thrombocytopenia.

Corticosteroids are not usually helpful in the treatment of acute granulocytic leukemia; there is even some evidence to suggest that they may actually make the condition worse.[50,51] Nevertheless, in severely toxic patients or in those who are bleeding, small doses of steroids may produce a sense of well-being and control hemorrhagic manifestations. The primary disease itself is unaffected.

Recent evidence suggests that corticoids may cause regression of metastatic breast carcinoma even when the patients are resistant to androgens and estrogens.[52] Apparently the hormones have to be administered for 2 to 3 months before objective evidence of tumor regression may be observed. Subjective benefit, manifested by a sense of well-being and increased appetite, may be seen within a day or two after the institution of therapy.

Perhaps the greatest use of corticosteroids in malignant disease is in the management of the secondary hemolytic anemia, which is not an infrequent complication, particularly in the lymphomas. Studies of the anemia of neoplastic disease have shown that it is frequently of a hemolytic nature[53,54] and may readily be controlled by small doses of steroids. In some patients with carcinoma, however, doses of prednisolone up to 100 mg. or more daily may be necessary to control the anemia.

It should be pointed out that steroids are not without their harmful effects in malignant disease. We have seen a number of patients who developed over-

whelming septicemia during hormone therapy. In addition, it is our impression that herpes zoster, a fairly common complication of malignant disease, occurs more frequently in patients on steroid therapy.[55] Finally, while this is difficult to establish on a statistical basis, we have the impression that the malignant process may be accelerated in some cancer patients during steroid therapy, resulting in more rapid dissemination of the disease. This is not entirely unexpected, since steroids are known to be potent lympholytic agents. With dissolution of lymph nodes, which may have trapped tumor cells, the ability of these cells to disseminate throughout the body may be enhanced. The administration of adrenocortical hormones, therefore, should be specific in cancer chemotherapy and not simply for "tonic" or euphoriant benefits.

II. Therapeutic Criteria.—

The agents of choice in various malignancies are outlined in Table II. The selection of the appropriate drug for a specific case, however, often requires less skill than does the election of the correct time for its administration. Since no chemotherapeutic agent presently available is curative and each drug has a time limit to its effectiveness, it is important to withhold chemotherapy for the appropriate indications. This concept is particularly true for hormones. For example, many patients with metastatic breast carcinoma may be managed satisfactorily with local radiotherapy to control solitary, symptom-producing metastases. Often the tumor grows at such a slow rate that specific therapy can be withheld for many months or even years.[47] In addition, since certain of the metastatic lesions respond more readily than others, treatment may better be withheld until metastases are fairly obvious and disseminated. On the other hand, a patient must not be allowed to progress to a "point of no return," since it is desirable that he be in good physical condition when therapy is instituted. Once hormone treatment is started it may be continued until resistance is obvious. At this point a new agent must necessarily be used in an attempt to induce another remission.

Cytotoxic and cytostatic compounds used to treat metastatic lesions should be started reasonably early during the course of the disease since the destruction of large tumor masses by a chemical agent would be most difficult. It is important to select a "target point" in dosage for each drug and to pursue treatment until the specified amount is given. Response to these drugs is slow and a minimum of one month should be allotted to each compound.

Specific indications for the mustardlike drugs have already been outlined. Newer cancer chemotherapeutic agents may find application in three general categories:

A. Intracavitary Administration of Alkylating Agents.—While malignant effusions can frequently be controlled by radioisotopes, the technique can be cumbersome and costly. Nitrogen mustard has been instilled in pleural and peritoneal cavities with considerable success.[56] The ethyleneimine compounds have also been effective[57]; we have found A-139 to be beneficial when instilled in the pleural or the peritoneal cavity. Since these drugs are not fixed to tissue as rapidly as is nitrogen mustard, benefit from intracavitary instillation may be somewhat delayed. When malignant effusion is the initial manifestation of recurrence or

TABLE II. PRINCIPAL INDICATIONS FOR ANTICANCER AGENTS

	CYTOTOXIC			CYTOSTATIC		CYTOLYTIC		
	NITROGEN MUSTARDS	ETHYLENE-IMINES	MYLERAN	FOLIC ACID ANALOGUES	PURINE ANALOGUES	ANDROGENS	ESTROGENS	ADRENAL HORMONES
Carcinoma.—								
Breast		+ +				+ + + +	+ + + +	+ +
Chorion	+ +	+ +		+ + + +				
Colon	+ +	+ +						
Kidney	+ +	+ +						
Lung	+ +	+ +						
Ovary	+ + +	+ +						
Pancreas		+ + +						
Prostate							+ + + +	
Stomach		+ +						

| | | |

spread of a malignant disease, it is our experience that intracavitary administration of one of these drugs may serve as a testing ground for its relative efficacy. If the effusion is controlled by the administration of this compound, a trial of systemic administration is begun. AB-100, the "dual antagonist," may be of particular value in this situation since it is less irritating than most of the available alkylating agents. The technique is simple and can be carried out by any physician, even on an outpatient basis.

B. Postoperative Prophylactic Chemotherapy.—In recent years a considerable amount of work has been done to demonstrate the dissemination of malignant cells in the blood following surgical manipulation and its control by nitrogen mustard and other cytotoxic agents,[58,59] but such prophylactic chemotherapy has not gained widespread trial. As soon as we have more effective drugs, this procedure will probably become routine. For the present, postoperative chemotherapy would seem indicated for the following categories of patients: (1) patients with known metastases that could not be removed at the time of operation; (2) patients in whom adequate surgical excision could not be carried out; (3) patients with bronchogenic carcinoma and gastric carcinoma (even when an adequate resection has been performed, since these tumors have a notoriously poor cure rate); (4) and finally, patients with regional lymph node involvement, particularly breast carcinoma. It is well known that once the axillary nodes are involved in breast carcinoma, the cure rate is markedly reduced. By use of contrast visualization of lymph nodes it has been demonstrated that lymphaticovenous communications may occur along the course of lymphatics.[60] Thus, once the nodes are involved, it is quite probable that tumor cells have already spread from the afferent lymph channels to adjacent venous drainage areas even before the regional node itself is able to trap the tumor cells. This is particularly true of the axillary lymphatic system.

C. Palliation of Disseminated Neoplastic Disease.—As new drugs are developed, it will always be necessary to "screen" them for their relative efficacy. The probability is that, as in bacterial chemotherapy, no one drug will be effective against all cancers; it will be necessary to test each drug against a variety of tumors to determine its relative value.[61] Although good results cannot reasonably be expected in far-advanced human neoplasms, these are the cases in which screening of new drugs is necessary. In our experience it is a rare patient or family who do not desire a trial of some investigative drug even when the inherent danger of such experimentation is explained.

One immediate application for new chemotherapeutic agents might be in combination with agents already proved to be of value but not curative by themselves. For example, once a hormone is shown to be effective against breast cancer in an individual patient, a cytotoxic drug could be added to the regimen in an attempt to destroy the non-hormone-dependent cancer cells, with a goal toward complete eradication of the tumor and its metastases. Some investigations along this line have already been reported.[62]

III. Signposts and Pitfalls.—

It is generally agreed that routine hematologic laboratory studies must be performed at regular intervals in patients receiving cytotoxic drugs. A helpful

laboratory aid is the sedimentation rate performed at monthly or bimonthly intervals. In patients with metastatic disease, the sedimentation rate of the erythrocytes is usually elevated, sometimes to a striking degree. If the antitumor chemical is effective there may be an appreciable decrease in the sedimentation rate. Conversely, recurrence of metastases may be anticipated when the sedimentation rate begins to rise.

Reticulocyte counts and bone marrow examinations prior to institution of therapy are important. We have observed a number of cancer patients with occult hemolytic anemia which was compensated by erythroid hyperplasia of the marrow and thus not clinically detectable as anemia. Following administration of one of the cytotoxic agents, the bone marrow becomes somewhat depressed and may not be able to compensate for the shortened red cell life span. Anemia then becomes overt and is ordinarily felt to be an indication for discontinuation of therapy. However, by administration of steroids in some cases, the anemia may be improved and the alkylating agent may be continued. Certain other information may be obtained by careful bone marrow scrutiny, namely, varying degrees of infiltration by tumor cells and a rough estimation of relative bone marrow activity, both of which may be used as a guide to therapy.

A word of caution should be given about the sudden development of leukopenia in a patient receiving cytotoxic drugs. All too often the loss of circulating leukocytes is attributed simply to excessive bone marrow depression. In our experience it may be a warning sign of serious infection. Fever may be absent as a result of the deficiency of granulocyte-pyrogens.[63] The mechanism of the leukopenia may be similar to that described above for anemia, namely, inability of the bone marrow to compensate adequately for the stress of infection due to partial suppression from chemotherapy.

SUMMATION

What is the role of the cancer chemotherapist in the conquest of malignant disease? Certainly the administration of chemicals to patients seems far removed from the basic research to discover the cure for cancer. Otto Warburg[5] has said, "The problem of cancer is not to explain life, but to discover the differences between cancer cells and normal growing cells. Fortunately this can be done without knowing what life really is. Imagine two engines, the one being driven by complete and the other by incomplete combustion of coal. A man who knows nothing at all about engines, their structure, and their purpose, may discover the difference. He may, for example, smell it."

It is the hope of the cancer chemotherapist that he may develop a perceptiveness in the use of antitumor agents which will enable him to "smell" something of value—perhaps the clue to the eventual conquest of malignant disease!

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Book Reviews

NEUROPHARMACOLOGY. Transactions of the Fifth Conference. May 27-29, 1959, Princeton, N. J. Edited by Harold A. Abramson, M.D. New York, 1960, Josiah Macy, Jr. Foundation. Pp. 251, indexed. Price $6.00.

This last in a series of conferences on neuropharmacology is in some ways the most interesting. The lead-off paper and discussion, which occupy half of the volume, constitute a stimulating contrapuntal exercise led by Dr. Udenfriend, who emerges as the outstanding virtuoso. His speculations and recommendations regarding amine metabolism and its pharmacologic implications are provocative while at the same time appearing eminently sensible. The Killams then present their exciting work on the neurophysiologic effects of potent tranquilizers and the electroencephalographic correlates of behavior. The other papers and the summations make for less rewarding reading, but the entire report of the conference is worth perusing for those interested in central nervous system drugs and neurohumors.

Louis Lasagna

EPILEPSY AND RELATED DISORDERS. Volumes I and II. By William Gordon Lennox. A.B., A.M., M.D., Sc.D. (Hon.), with the collaboration of Margaret A. Lennox, A.B., M.D. Boston and Toronto, 1960, Little, Brown & Company. Pp. 1,168. Price $13.50 for two volumes.

The name of Dr. Lennox has been closely linked with epilepsy, both in professional and lay minds, during the past 30 years. His many studies, with a number of collaborators, of physiologic factors such as blood flow and metabolic changes associated with seizures are well known. The pioneering electroencephalographic correlations established by the group need no emphasis, neither do the informative genetic studies of afflicted twins. Enthusiastic and productive drug trials were inevitable for one so interested in the personal and sociologic impact of seizures on the individual.

It is, therefore, highly fit and timely that this distillation of his long clinical experience, broad historical interests, and fervent social conscience should be available to all interested in epilepsy. Viewed in this sense, these volumes form a very real and delightful addition to medical literature. The subject matter, copiously sprinkled with ancedotes, ranges from pertinent historical references, through clinical patterns, drug actions, and genetics, to broad legal and sociologic considerations. These volumes must not, of course, be considered instructional or critical reviews in any sense, and criticisms based on those approaches would be irrelevant.

J. W. Magladery

LEUKAEMIA. RESEARCH AND CLINICAL PRACTICE. By F. G. J. Hayhoe, M.A., M.D., M.R.C.P. Boston, 1960, Little, Brown & Company. Pp. 335, indexed. Price $16.00.

Dr. Hayhoe states in the preface to this volume, "My intention in writing this book has been to provide a guide through the maze of published work to separate the tangled lines of progress in research and to give in small compass, a reasonable comprehensive survey of current beliefs and activities in both laboratory and clinical aspects of leukaemia."

These objectives are quite ambitious, considering the vast amount of past and current work in this area; but despite the enormity of the task, the author manages to fulfill his promise in a very lucid manner.

The book is divided into four sections. The first is concerned with general aspects such as history, classification, statistics, and experimental studies regarding the etiology of leukemia.

The second section provides a valuable summary of cytology, biochemistry, and immunology with respect to the leukemia cell. There is, in addition, a chapter devoted to in vitro culture studies.

The last two sections deal with various clinical aspects and the principles of therapy and management. The organization and presentation of this material are particularly good. Case reports are carefully chosen to illustrate various points. The book concludes with a discussion of leukemoid reactions and paraleukemic states.

A book of this type is necessarily out of date by the time it is published. Nevertheless, this volume presents a fairly comprehensive, clear distillate of the experimental and clinical leukemia literature up to mid-1958. The bibliography is well chosen and adds greatly to the value of the work. The printing and illustrations are good. The book is highly recommended for the clinician and the laboratory worker interested in leukemia.

George W. Santos

AN INTRODUCTION TO PHARMACOLOGY. By J. J. Lewis. Edinburgh and London, 1960, E. & S. Livingstone, Ltd. Pp. 826, indexed. Price $11.00. (Williams & Wilkins Company, Baltimore, exclusive U. S. agents.)

Vol. 13
1961

An Introduction to Pharmacology is an excellent textbook for medical students. Lewis writes informatively but concisely about each group of drugs, and his book concentrates on action and mechanism of action as a function of chemical structure to a greater extent than most student textbooks. The introduction, though short, is a lucid presentation of the problems and techniques of basic pharmacology.

The book provides easy, enjoyable reading; the author has expounded on his subject in a deliberately didactic way and has excluded most of the controversy inherent in any growing science. In spite of this, the book is quite up to date.

I should certainly recommend *An Introduction to Pharmacology* to teachers who are preparing to introduce students to this discipline for the first time, either as a guide to their lectures or as a supplement.

John B. Murphy

SYMPOSIUM ON SALT AND WATER METABOLISM. Alfred P. Fishman, M.D., Guest Editor. New York, 1959, American Heart Association. Pp. 805-1060. Price $2.00.

In December, 1959, the New York Heart Association sponsored a symposium on salt and water metabolism, the substance of which is now available in this volume. The last few years have seen important changes in our views about certain aspects of this field, particularly with reference to renal function, and these are reflected by the articles in the symposium.

The symposium begins with the theory of solutions. R. J. Podolsky discusses in his typically lucid way the structure of water and electrolyte solutions. Podolsky emphasizes the "ice-like-ness" of liquid water, its lattice structure, and the possible import of this fact on electrolyte transport. Irving Klotz has a particularly fine review of the interactions of protein molecules in solution, and Alexander Mauro discusses some properties of ionic and nonionic membranes. Mauro's task is in many ways the most difficult of the three in this section, and although his contribution is a splendid introduction to the subject, the limits imposed on him by the symposium forced him into brevity in certain areas which the reader may not find clear.

One of the most fruitful recent hypotheses in the field of renal function is that concentration of urine is effected by a countercurrent mechanism, in consequence of the hairpin structure and permeability of nephrons, a proposal first made and supported by Hargitay, Kuhn, and Wirz. The importance of this hypothesis is reflected by several articles in the symposium, particularly by Carl Gottschalk's clear discussion of osmotic regulation in the mammalian nephron, based largely on an interpretation of his own micropuncture studies of nephrons in terms of the countercurrent hypothesis.

Nephrologists have also recently entered the bioelectric theater. The inside of tubular cells is electrically negative to the outside, and the tubular lumen is negative to the peritubular fluid. Gerhard Giebisch has reviewed the information available in this relatively new field, a good deal of which is his own, and interpreted it in a way which is now classic for the case of electrical potential differences across cells of other organs and tissues.

A few years ago, Walter Wilde and his colleagues discovered that, if urine flow was stopped momentarily, the urine obtained shortly after release of the obstruction exhibited sequential changes in concentration, as a function of flow, that could be interpreted in terms of the function of different parts of the nephron and collecting ducts. The subject is reviewed well by Malvin and Wilde in this symposium.

Robert Berliner marshals the evidence for interexchange of sodium, potassium, and hydrogen across the nephron, a mechanism which he first postulated and which is of great importance in urinary acidification.

The symposium closes with reviews of various phases of extrarenal regulation of salt and water metabolism, including the question of volume receptors, adrenoglomerulotropin, aldosterone, antidiuretic hormones, transport in the gut, the eye and the bile, the avian salt-secreting gland, and the relation of mucopolysaccharides to sodium metabolism. All are especially good for the general reader as well as for toilers in the vineyard. This is one of those rare symposia that deserve to be published.

Kenneth L. Zierler

DETOXICATION MECHANISMS. THE METABOLISM AND DETOXICATION OF DRUGS, TOXIC SUBSTANCES AND OTHER ORGANIC COMPOUNDS. Second edition. By R. Tecwyn Williams, Ph.D., D.Sc. New York, 1959, John Wiley & Sons, Inc. Pp. 796, indexed. Price $19.00.

In 1947, when this book first appeared, xenobiochemistry (the biochemistry of organic compounds foreign to the organism) was in a relatively fragmentary state. Professor Williams nevertheless contributed, in that first edition, a unique volume which no self-respecting pharmacology laboratory could afford not to have on its shelves. Today, over a decade later, the second edition is almost three times larger and embodies not only empirical chemical data but also a good deal of material bearing on enzymatic mechanisms. Those interested in pharmacology or toxicology are advised to put in their orders now.

Louis Lasagna

PHYSIOLOGY OF THE RETINA AND THE VISUAL PATHWAY. By G. S. Brindley, M.A., M.D. (Monographs of the Physiological Society, No. 6) London, 1960, Edward Arnold Ltd. Pp. 298, indexed. Price $7.50. (Williams & Wilkins Company, Baltimore, exclusive U. S. agents.)

In addition to electrophysiology, this book covers the photochemistry of retinal pigments and, in the last half, the wide range of human sensory observations from which one can infer visual mechanisms. It is probably the best compendium on visual function since Willmer's book of 1946, weaving in the recent work of Hubel and Kuffler. Lacking is any discussion of the tremendous organization of the retinal bipolars, whose interconnections must profoundly affect any theory of brightness or color vision, and, correspondingly, the alternative (Hering-Jameson) theory of chromatism, more flexible than the tricolor and providing a place for bipolar function. However, Brindley's book is an excellent basis for one entering research in visual physiology, in its balanced treatment of the multiple factors.

S. A. Talbot

EXPERIMENTS IN HEARING. By Georg von Békésy. Translated and edited by E. G. Wever. New York, 1960, McGraw-Hill Book Company, Inc. Pp. 746, indexed. Price $25.00.

This book is a collection of von Békésy's major papers. The book contains an introductory section on the anatomy of the ear and experimental techniques, followed by sections on "The Action of the Middle Ear," "Bone Conduction," "Auditory Thresholds," "The Spatial Attributes of Sound," "Problems of Distortion," "Room Acoustics," "The Pattern of Vibrations in the Cochlea," "Wave Motion in the Cochlea," "Frequency Analysis and the Law of Contrast" (largely presenting von Békésy's works on similarities between auditory and cutaneous phenomena), and "The Electrophysiology of the Cochlea."

Much of the work presented in these papers represents the core of those aspects of current auditory theory and practice dealing with the system from the production of the sound wave to the initiation of auditory nerve impulses. In addition, von Békésy's description of the functioning of the peripheral receptor system is basic to an understanding of central nervous mechanisms of audition. The studies are described with the meticulous attention to detail that is also evident in the conduct of von Békésy's experiments.

As a collection of the works of one man, this book is not intended to present a complete overview of audition or even of the topics covered. Consequently, there may be created many false impressions in the reader who does not have some sophistication in the areas dealt with. For example, the work of Wolff and her associates indicates other possible forms of vibration of the eardrum than that described by von Békésy. The treatment of the relation of the stimulus frequency spectrum to the perception of the distance of a sound source is limited to relatively small distances (i.e., spherical wave fronts), with the considerable efforts of other workers pertaining to larger distances receiving no mention. In the sections on electrical phenomena in the cochlea, the contributions of Davis and his co-workers are largely ignored.

This incompleteness is comparatively more serious in areas where von Békésy's work represents a smaller portion of the total effort, as, for example, in the sections on "Auditory Thresholds" and "Spatial Attributes of Sounds." In the area of cochlear mechanics, where von Békésy's work is supreme, the omission of the works of others does not materially distort the picture, although the problem of the mode of transmission of energy in the cochlea does not receive the complete coverage devoted to other problems.

The reader who is looking for a comprehensive review of the areas treated in this book is, therefore, cautioned not to rely solely on this volume. He can, however, ill afford to ignore this collection of excellent studies.

Paul D. Coleman

COMMUNICABLE AND INFECTIOUS DISEASES. By Franklin H. Top, A.B., M.D., M.P.H., F.A.C.P., F.A.A.P., F.A.P.H.A., and collaborators. St. Louis, 1960, The C. V. Mosby Company. Pp. 812, indexed. Price $20.00.

In the preface, the author states, "This book is intended as a text or handy reference for all persons whose professional duties necessitate contact with certain communicable diseases or infestations." It is difficult to know whether or not the book serves this purpose. Most of the chapters are no more comprehensive than those in standard textbooks of medicine, and in some instances the chapters are not as adequate as some in texts not devoted exclusively to communicable and infectious diseases. I doubt very much that one would turn to a text of this type to study these diseases. Its use, therefore, is more as a guide for the uninformed or for those who need to know only the major features of the diseases, including primarily persons other than physicians. Many of the chapters are good as far as they go, but as the definitive statements on disease that one expects to find in a specialized text, they leave much to be desired. The book cannot be recommended to medical students or physicians but might be of use to public health officers, hygienists, sanitary engineers, and nurses.

Leighton E. Cluff

Announcements

Scheduled to appear in 1961 is a SYMPOSIUM ON HYPOTHYROIDISM including the following papers:

1. Hypothalamic and Pituitary Function as Related to the Thyroid, S. A. D'Angelo, Jefferson Medical College, Philadelphia, Pennsylvania.
2. Iodine Metabolism and Thyroid Physiology, John Stanbury, Massachusetts General Hospital, Harvard University, Boston, Massachusetts.
3. The Metabolism of Thyroid Hormones as Related to Protein Binding, Sidney Ingbar, Thorndike Memorial Laboratory, Harvard University, Boston, Massachusetts.
4. Fluid and Electrolyte Abnormalities in Hypothyroidism, Solomon Papper, Medical College of Virginia, Richmond, Virginia.
5. Protein and Carbohydrate Abnormalities in Hypothyroidism, Kenneth R. Crispell, University of Virginia Hospital, Charlottesville, Virginia.
6. Cholesterol Metabolism in Hypothyroidism as Related to the Newer Thyroid Analogues, Marvin Sachs, University of Pennsylvania, Philadelphia, Pennsylvania.
7. Thyroiditis as Related to Hypothyroidism, Charles Short, King's College, Durham University, Newcastle-upon-Tyne, England.
8. The Diagnosis and Treatment of Primary and Secondary Hypothyroidism, John Wiswell, University of Maryland, Baltimore, Maryland.
9. The Heart in Hypothyroidism, Milton Hamolsky, Beth Israel Hospital, Boston, Massachusetts.
10. Myxedema, Neuropathy and Myopathy, Stuart Nichols and Boyd Frame, Henry Ford Hospital, Detroit, Michigan.
11. Hypometabolism and Low Thyroid Reserve, William Jeffries, Western Reserve University School of Medicine, Cleveland, Ohio.

THE AMERICAN ACADEMY FOR CEREBRAL PALSY held its Thirteenth Annual Meeting in Pittsburgh, Pennsylvania, at the Penn-Sheraton Hotel, Oct. 5 through 7, 1960. The newly elected officers for 1960-1961 are as follows:

G. W. N. Eggers, M.D., President
2201 Market St.
Galveston, Texas

Russell Meyers, M.D., Vice-President
University Hospital
Iowa City, Iowa

Jessie Wright, M.D., President-elect
142 Bellefield Avenue
Pittsburgh 15, Pennsylvania

J. D. Russ, M.D., Secretary
1520 Louisiana Ave.
New Orleans 15, Louisiana

Samuel B. Thompson, M.D., Treasurer
5520 W. Markham
Little Rock, Arkansas

The 1962 Annual Meeting will be held in St. Louis, Missouri, at the Chase and Park Plaza Hotels on Nov. 9 to 11, 1962.

A PROGRAM OF GRADUATE TRAINING FOR RESEARCH INVOLVING SOCIAL SCIENCE IN MEDICAL CARE is offered by the Bureau of Public Health Economics, School of Public Health, The University of Michigan, Ann Arbor. The program, now in its second year, was set up in recognition of the growing demand for social scientists in the various health and medical care fields. Medicine, public health, economics, sociology, and social psychology are represented on the Bureau staff.

Graduate assistantships, research assistantships, and predoctoral fellowships are available. For further information write to

Dr. J. S. Axelrod, Director
Bureau of Public Health Economics
School of Public Health, University of Michigan
Ann Arbor, Michigan

Applications must be submitted before Feb. 1, 1961, for the fall semester.

INFLUENZA IMMUNIZATION (excerpts from a statement by Leroy E. Burney, Surgeon General, Public Health Service, published in *Public Health Reports* 75:944, 1960, and from a letter from Dr. Burney to the Editor).

"Two outbreaks of influenza swept the United States in the fall of 1957 and the winter of 1958, resulting in 60,000 more deaths than would be expected under normal conditions. There were, in addition, more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

"These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent such an occurrence in the future.

"The Committee found that a new antigenic variant, the Asian strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths, not only in the total population but most markedly among the chronically ill, the aged, and pregnant women.

"If, as vaccine trials have indicated, the influenza vaccine may be assumed to be 70 per cent effective in preventing the disease, then it may be estimated that approximately 60,000 of the 86,000 excess deaths during influenza epidemics of the past three years might have been prevented by adequate immunization.

"As a result of these findings, the Public Health Service is urging a continuing program to protect these high-risk groups in order to prevent a recurrence of this excess mortality.

"The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

"1. Persons of all ages who suffer from chronic debilitating disease, in particular: (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.

"2. Pregnant women.

"3. All persons 65 years or older.

"The adult dosage recommended by the advisory committee for initial immunization is 1.0 cc. (500 cca units) of polyvalent vaccine, administered subcutaneously on two occasions separated by two or more months. Preferably, the first dose would be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1.0 cc. subcutaneously each fall, prior to November 1. The only contraindication to vaccination would be a history of food allergy to eggs or chicken or a prior history of allergic reaction to an egg-produced vaccine, such as the commercial influenza product.

"The time to start such a program is before the onset of the influenza season this fall. In the past, influenza vaccination has been sparse and sporadic, and primarily in response to an epidemic or the threat of an epidemic. The unpredictability of recurrence of influenza and its continued

endemic occurrence are well known. Therefore, the Public Health Service strongly recommends that immunization of these high-risk groups be started now and continued annually, regardless of the predicted incidence of influenza for specific years.

"Copies of an illustrated brochure, *Asian Influenza, 1957-60*, may be obtained from the Communicable Disease Center, Atlanta 22, Ga."

THE MARY PUTNAM JACOBI FELLOWSHIP COMMITTEE of the Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to any graduate woman physician. The $1,000.00 fellowship will begin Oct. 1, 1961, for a period of one year. At the discretion of the Committee, an award of $2,000.00 may be given biannually. The fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the fellowship, but exception may be made under special circumstances.

Application forms may be obtained from Ada Chree Reid, M.D., Chairman, 118 Riverside Drive, New York 24, N. Y.

Applications must be returned before March 1, 1961.

TRAINING PROGRAM FOR STEROID BIOCHEMISTRY is announced for 1961-1962 by The Worchester Foundation for Experimental Biology, Shrewsbury, Massachusetts, with The Department of Chemistry, Clark University, Worchester, Massachusetts, and The Department of Biochemistry, College of Medicine, University of Utah, Salt Lake City.

Under the sponsorship of the National Cancer Institute, National Institutes of Health, United States Public Health Service, specialized programs have been established in the above-mentioned departments to train investigators in the theoretical and methodologic aspects of the biochemistry of steroids and related compounds. Each program includes lectures, planned laboratory work, and research.

Postdoctoral candidates (M.D. or Ph.D.) selected for admission at either university will receive stipends of $5,500.00 for a one-year period. Predoctoral candidates (B.S., M.S., or equivalent) selected for admission (at Worcester only) will receive stipends of $1,800.00 for a six-month period.

Application forms and further information may be obtained from either of the following:

Dr. Kristen Eik-Nes
Department of Biochemistry
College of Medicine
University of Utah
Salt Lake City, Utah

Dr. William R. Nes
Department of Chemistry
Clark University
950 Main Street
Worchester, Mass.

The final date for completion of application is June 1, 1961. Classes begin Oct. 1, 1961.